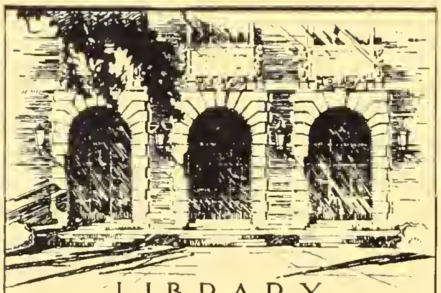

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ORGANIC SEMINAR ABSTRACTS

1964-65

Semester I

Department of Chemistry and Chemical Engineering

University of Illinois

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ORIENTATION IN SODIUM AND POTASSIUM METALATIONS OF AROMATIC COMPOUNDS

Reported by Earl G. Alley September 28, 1964

Metalations of aromatic compounds by sodium or potassium may be accomplished by several general reactions, as follows:

i. $RM + ArH \rightarrow RH + ArM$
ii. $ArH + M \rightarrow ArM + 1/2\ H_2$
iii. $ArX + 2M \rightarrow ArM + MX$
iv. $ArOR + 2M \rightarrow ArM + ROM$
v. $ArM' + M \rightarrow ArM + M'$

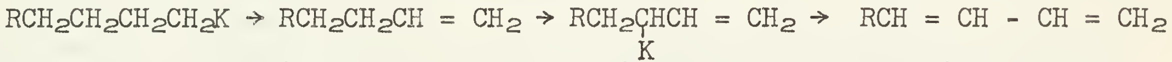
Most of the mechanistic investigations have involved the first of these reactions, specifically with sodium or potassium alkyls as metalating agents. There are several general reviews in the literature (1, 2, 3, 4) dealing with organosodium and organopotassium compounds.

The Nature of Organosodium and Organopotassium Compounds - The alkyl and aryl compounds of sodium potassium are nonvolatile, practically insoluble in hydrocarbons, and do not have sharp melting points. These facts have been cited (1) as evidence that the carbon-metal bond in these compounds is ionic. In contrast, organolithium compounds are volatile and soluble in hydrocarbons (3). It has been proposed (5,6) that the carbon-lithium bond has considerable ionic character. The difference in properties may be due to the tendency (3) of alkyllithium to be highly associated.

Alkylsodium and alkylpotassium are highly reactive substances. Under conditions similar to those employed in the metalation reactions, they have been shown (7, 8) to undergo a number of decomposition reactions:

$$RCH_2CH_2K \rightarrow RCH = CH_2 + KH$$

$$RCH_2CH_2K \rightarrow RK + CH_2 = CH_2$$



$$RCH_2CH_2CH_2CH_2K \rightarrow RCH_2CH_2CH = CH_2 \rightarrow RCH_2\underset{K}{C}HCH = CH_2 \rightarrow RCH = CH - CH = CH_2$$

by such processes a great variety of organopotassium compounds may arise and thus the identity of the actual metalating agent may be unknown. Alkylsodium compounds are much less reactive (8) than the corresponding potassium derivatives and these decomposition reactions are of little importance under the conditions used in aromatic metalations with alkylsodium. Finnegan (9) has observed that butyl- and amylpotassium will metalate such hydrocarbons as pentane, hexane, and cyclohexane. Often these or similar substances are used as solvents in the preparation of organopotassium compounds to be used as metalating agents. Thus the actual alkyl group in the metalating agent in these cases may be derived from the solvent rather than from the expected source.

Metalation of Aromatic Hydrocarbons - In all of the experiments the metalation products were identified by carbonation, followed by quantitative analysis of the mixture of acids thus obtained.

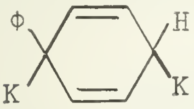
Bryce-Smith separated these acid mixtures by the following methods: When benzene was metalated (10), benzoic acid was isolated by extraction with benzene, and isophthalic and terephthalic acids were separated by crystallization of the methyl esters. When alkylbenzenes were studied (11, 12) the acids from the carbonation were first oxidized to benzoic and phthalic acids and then separated by means similar to those above. No satisfactory method for separating phthalic acid was found, so the amount of the acid mixture that was not isolated as benzoic, isophthalic or terephthalic acids was assumed to be phthalic acid. Benkeser and coworkers could find no indication (13, 14, 15) of ortho substitution in similar experiments, in which they analyzed (13, 14, 15) the acid mixtures they obtained from carbonation by conversion to the corresponding methyl esters and vapor phase chromatography of these esters. Control experiments proved this method to be very reliable. In cases where Bryce-Smith's (12) and Benkeser's (15) data overlap there was good agreement between the two analytical methods.

It is possible that the mixture of acids obtained from carbonation of the re-

action mixtures does not reflect the true ratios of organometallic isomers present. No controls were made to study this possibility by either Bryce-Smith or Benkeser. Russell has reported (16) that α-cumylpotassium upon treatment with deuterium oxide yields a product which has deuterium only in the side chain. Ziegler and Schnell reported (17) that carbonation of 1,1-diphenylethylpotassium produces only 2,2-diphenylpropionic acid in 80 to 90% yield. Benkeser has shown (14) that *p*-chloroethylbenzene when treated with potassium in decane for one hour followed by carbonation yields only *p*-ethylbenzoic acid. These results indicate that the products of the carbonation do reflect the isomer distribution in the organometallic mixtures.

The metalation of benzene was first reported (18) by Schorigin. Ethylsodium was the metalating agent employed. Gilman and coworkers investigated (19) the reaction and reported that in addition to phenylsodium, small amounts of *ortho* and *para* dimetalated benzene occurred. Morton and coworkers reported, (20, 21) that dimetalation of benzene with *n*-amylsodium yields 80% or *meta* and 20% or *para* isomers and they interpreted (1) these results in terms of an electrophilic substitution mechanism for the reaction. Bryce-Smith and Turner (10) attempted to clarify the contradictory results of Gilman and Morton. They found that action of ethylsodium on benzene produces *para* and *meta* disubstitution in a ratio of about 7:3. In this same work potassium metalation was also investigated. The alkyl group of the metalating agent was varied, and although some changes in the *para* to *meta* ratio were noted, no logical relationship was obvious. In all cases, *para* and *meta* disubstitution predominated. The metalating agent was produced by reaction of an alkyllithium with potassium. The reagent thus formed is an alkyllithium-alkylpotassium complex. The reactivity of such complexes is intermediate between those of alkyllithium and alkylpotassium compounds. Morton and Claff have investigated (22) the effect of alkoxide ion on the dimetalation of benzene. The alkoxide is thought (22) to form an ionic aggregate with the metalating agent. The effect of alkoxide was to increase the ratio of *meta* to *para* dimetalation from 3:1 in the absence of alkoxide to values that ranged from 3.3:1 for sodium cyclopentoxide to 50:1 for lithium *t*-pentoxide.

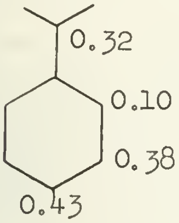
Morton and Lanpher assigned (23) the reaction product of benzene with phenylpotassium structure I. Evidence for this structure was absorption at 1165 cm.$^{-1}$ in the infrared spectrum, which is also observed (24) in the spectra of benzyl, α-methylbenzyl, and α,α-dimethylbenzyl anions. No assignment of these bands was made so this evidence may not be valid support for structure I. Pyrolysis of I yielded biphenyl, and carbonation of I gave a diacid, which upon pyrolysis yielded *p*-phenylbenzoic acid. The behavior of I upon pyrolysis provides evidence against metalation mechanism D, page 5 .



I

Orientation in the metalation of alkylbenzenes has been surrounded by considerable confusion. Schorigin (25) studied the metalation of toluene, ethylbenzene, and cumene. He reported that metalation with ethylsodium occurred in the α-position of the side chain. Morton and coworkers reported (26) that *n*-amylsodium attacked cumene *para* and *ortho* to the isopropyl group. This result was interpreted (1, 26) as evidence for an electrophilic substitution mechanism for the reaction. Bryce-Smith has made a detailed study (11) of the metalation of alkylbenzenes including the effects of changes in temperature and reagent on the reaction. Ethylpotassium, the metalating agent in this study, was prepared from alkyllithium and potassium and therefore the actual reagent is an alkyllithium-alkylpotassium complex (11). It was found that α-attack decreased in the order toluene $>$ ethylbenzene $>$ isopropylbenzene. For toluene attack in the α-position was 100%, for ethylbenzene 50%, and for isopropylbenzene 13% of the total substitution. This order of reactivity parallels the stability of the benzylic anions (27, 28) of these alkylbenzenes, so these data provide evidence for metalation mechanisms B and C, page 4 . The effect of substituents on nuclear metalation was also investigated (11). The competitive metalation of benzene and isopropylbenzene, and benzene and *t*-butylbenzene were studied. The metalating reagent was ethylpotassium formed from ethyllithium and potassium metal. For isopropyl-

benzene, the total rate factor for nuclear and α-metalation was 0.28 and for t-butylbenzene 0.19. Although no method was indicated Bryce-Smith evidently calculated these rate factors by multiplying n_A/n_B by $6/x$, where n_B and n_A are the number of moles of acid derived from benzene and the alkylbenzene respectively and x is the number of hydrogen atoms in the alkylbenzene that may be metalated (β-hydrogens are not counted). The partial rate factors for isopropylbenzene are indicated in II. For t-butylbenzene the partial rate factor for para substitution was 0.4. The meta isomer from t-butylbenzene could not be isolated. Bryce-Smith (12), using ethylsodium to metalate isopropylbenzene, found the total rate factor to be 0.24, which agreed well with the value obtained with ethylpotassium. Temperature and the method of preparation of the metalating reagent were found (11) to have little effect upon the isomer distribution. Benkeser and coworkers have studied the reactions of isopropylbenzene (13, 15) and ethylbenzene (14) with n-amylpotassium and n-amylsodium in excess alkylbenzene. Some of the results of these experiments are given in Tables I and II. These data agree fairly well with the findings of Bryce-Smith (11,15). The same order of reactivity (ethyl > isopropyl) in the α-position relative to the nuclear positions was observed by both investigators and both workers found nuclear metalation to be predominantly meta and para.



II

Table I

Metalation of Isopropylbenzene with n-Amylpotassium and n-Amylsodium

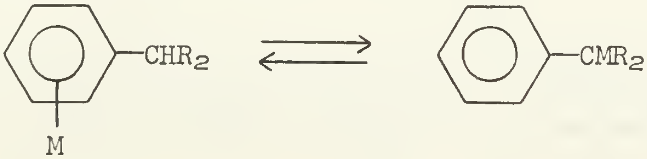
Metalating Agent	Reaction Time in Hours	% Yield of Methyl Esters	Product Composition α	m	p
1. n-amylsodium	20	48	2	55	43
2. n-amylsodium	48	10	10	27	27
3. n-amylpotassium	20	49	88	4	8
4. n-amylpotassium	48	56	100		
5. n-amylpotassium	3	-	42	39	19

Table II

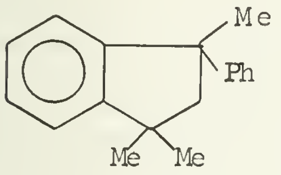
Metalation of Ethylbenzene with n-Amylpotassium and n-Amylsodium

Metalating Agent	Reaction Time in Hours	% Yield of Methyl Esters	Product Composition α	m	p
1. n-amylsodium	3	32	18	52	30
2. n-amylsodium	20	46	68	19	13
3. n-amylpotassium	20	31	100		
4. n-amylpotassium	3	12	100		
5. n-amylpotassium	0.5	10	93	6	1

It is clear that when long reaction times are employed, α-isomer is being formed at the expense of meta and para isomers. This isomerization occurs with both isopropyl- and ethylbenzene but is more rapid with ethylbenzene. The interpretation given these data by Benkeser is that nuclear metalation occurs in a kinetically con-



trolled process and that isomerization occurs as depicted above, to the thermodynamically stable α-isomer. He postulates that the α-isomer derives this stability from resonance stabilization of the benzylic anion. Further evidence for this equilibrium is obtained from the reactions of *o*, *m*, and *p*-chloroethylbenzene with sodium in ethylbenzene. In each case the isomer distribution of the products was about 80% α, 10% *m*, and 5% *p*. Streitwieser and coworkers have shown (27) that the rate, relative to benzene-*t*, of lithium cyclohexylamide catalyzed exchange of tritium from the α-position of toluene is about 100 times faster than exchange with the nuclear positions of toluene. The rate of exchange at the α-position of isopropylbenzene was only about twice the rate of exchange of the nuclear positions of toluene. However, the nuclear positions of isopropylbenzene should be less reactive than the nuclear positions of toluene, so these data do provide evidence for the greater stability of benzylic anions over aryl anions. In Table I, experiment 2, side reactions predominated. An acid whose structure was shown to be 3-phenyl-3-butenoic acid was isolated from the carbonation mixture. The retention time of its methyl ester by vapor phase chromatography was identical with that of an authentic sample. This same acid was produced when α-methylstyrene was treated with *n*-amylsodium followed by carbonation. Traces of α-methylstyrene were detected in the carbonation products of experiment 2, Table I. Another substance detected in this reaction was 1,1,3-trimethyl-3-phenylindane III. The α-methylstyrene could arise from elimination of NaH from α-cumylsodium. Metalation of α-methylstyrene followed by carbonation would produce the 3-phenyl-3-butenoic acid that was observed. Dimerization of α-methylstyrene could produce 1,1,3-trimethyl-3-phenylindane III and has been shown (15) to do so when stannic chloride or α-cumylpotassium were employed as catalysts. The v.p.c. retention time and n.m.r. spectrum of III were identical with those of an authentic sample prepared by dimerization of α-methylstyrene. Under the same conditions (experiment 4, Table I) *n*-amylpotassium produces no such side reactions, which indicates that α-cumylsodium is less stable than the corresponding potassium compound. This is an exception to the usual order (8) of stability of alkylsodium and alkylpotassium.



III

Hydrogen isotope effects were reported (29) for metalation of benzene and toluene by Bryce-Smith and coworkers. Mixtures of benzene and deuterobenzene, benzene and mixed deuterobenzenes, and toluene and α-deuterotoluene were treated with a deficiency of ethyllithium-ethylpotassium complex. Toluene under these conditions undergoes (11) only α-metalation. The values of k_D/k_H were calculated from the amount of deuterium found in the carbonation products. These calculated values are listed in Table III. It is difficult to compare these values quantitatively because the experiments with benzene were conducted at higher temperatures than was the experiment with toluene, but the difference is too large to be attributed solely to the change in temperature.

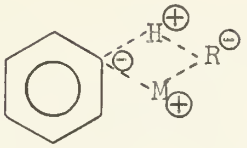
Table III

Hydrogen Isotope Effects in the Metalation of Benzene and Toluene

Starting Material	Temp. °C	% D in product atom %	k_D/k_H
C_6H_5D,C_6H_6,(15.30 at. %)	75	13.8	0.50 ± 0.1
Mixed Deuterobenzenes (7.8 at. %)	75	6.41	0.50 ± 0.1
α-deuterotoluene (12.50 at. %)	20	10.4	0.22 ± 0.05

Several mechanisms for the nuclear metalation reaction have been considered (11). They are as follows: A, electrophilic substitution; B, nucleophilic attack on hydrogen; C, a tetrapolar transition state IV in which both A and B are operating simul-

taneously; D, the addition of RM to the aromatic nucleus followed by loss of RH; and E, homolytic substitution.

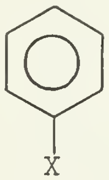


IV

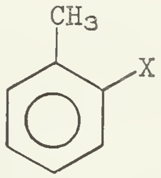
Bryce-Smith (11, 12, 29) and Benkeser (13, 14, 15) agree that either mechanism B, or mechanism C with B more important than A in the transition state, is compatible with the data. Mechanism A is eliminated (11) because the orientation and the rate factors do not fit this mechanism, from which one would expect *ortho* and *para* substitution of alkylbenzenes. *Meta* and *para* substitution were observed by Bryce-Smith (11, 12) and Benkeser and coworkers (13, 14, 15) (see Tables I and II). The alkyl substituents should cause increased reactivity if an electrophilic mechanism were operating, but the opposite is the case. These factors also exclude mechanism C where A is important. The objection to mechanism D is that in cases where such additions are known to occur, they are not followed by elimination of RH. One such case is the addition of phenylpotassium to benzene (23) page 2, in which potassium hydride was eliminated rather than benzene. Mechanism E was eliminated for the following reasons: The ease of hydrogen atom abstraction from benzene, ethylbenzene and isopropylbenzene (30, 31) is exactly opposite to the ease of metalation of these substances in the α-position as observed by Bryce-Smith (11). No bibenzyl compounds were detected (11) in the reaction products. In studies of homolytic phenylation of alkylbenzenes (32) the total rate factor for phenylation of isopropylbenzene is 0.87 and for metalation 0.28. Large amounts of *ortho* substitution occurred (32) in the phenylation reaction, 53% for ethylbenzene compared to complete absence of *ortho* isomer (14) in the metalation reaction. These data do not provide conclusive evidence against a homolytic mechanism, but they do provide indication against such a mechanism.

Mechanism B or mechanism C dominated by B is favored (11, 12, 29) for these reasons: The hydrogen isotope effect observed (29) requires that the breaking of the bond to hydrogen be involved in the rate determining step of the reaction. Mechanisms B and C meet this requirement, but the other mechanisms cannot be excluded by these data. The total rate factors (11) and the orientation of the substitution (11, 13, 14, 15) are in accord with the effect expected for a protophilic substitution reaction. The alkyl groups by inductive effects increase the electron density in the ring and thus decrease the acidity of the protons attached to it. The inductive effect of the alkyl group should cause greatest deactivation in the *ortho* and least in the *meta* and *para* positions.

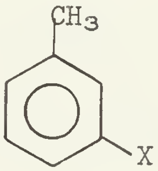
Investigations of the relative rates of exchange of the aryl hydrogens of toluene (28) by 0.2N potassium amide at 25° in ammonia show that the *ortho*, *meta*, and *para* positions have rate constants as indicated. The rate constants (28) for α-hydrogen



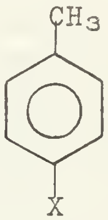
$10^6k = 490\ sec^{-1}$



$110\ sec^{-1}$



$220\ sec^{-1}$



$200\ sec^{-1}$

exchange in isopropylbenzene, ethylbenzene, and toluene ($C_{KND_2} = 0.02N$, 10°) are $10^5k = 4, 20,$ and $140\ sec^{-1}$ respectively. These trends in reactivity follow very closely those observed for metalation by alkylsodium or alkylpotassium. In mechanism B, the orientation would depend on the acidity of the respective hydrogen and close

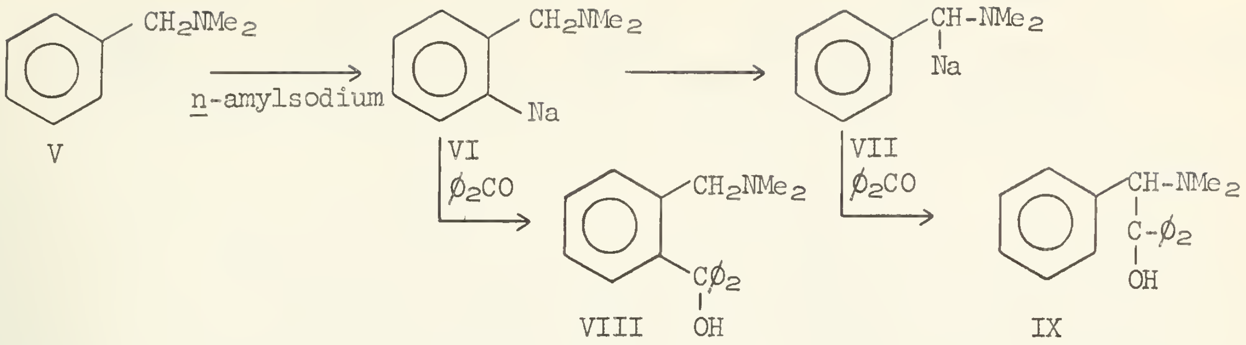
resemblance between the exchange reactions and the metalation reaction would be expected.

Morton does not favor (24) mechanism B, holding the view that it is the cation rather than the anion that profoundly affects the course of the substitution. The facts which he cites in support of this view are that in the case of cumene, α-substitution occurs when n-amylpotassium is the metalating agent and nuclear substitution predominates when n-amylsodium is employed. The data in Table I show that complete α-substitution of cumene is attained rapidly but that initially some nuclear metalation occurs and that isomerization to the α-isomer follows. The effect of cation on the reaction appears to result from its influence upon the rate of this isomerization. This influence evidently arises from the greater stability of benzylic anions associated with potassium as opposed to those associated with sodium. The greater stability of α-cumylpotassium over α-cumylsodium is also indicated from the observation (15) (Table I), that metalation of cumene with n-amylsodium results in side reactions other than isomerization to the α-isomer. Metalations of polynuclear hydrocarbons are known (2, 3, 4) but they do not shed additional light on the mechanism.

Metalation of Compounds other than Aromatic Hydrocarbons - The metalation of various alkylferrocenes has been studied (33, 34). Nesmeyanov and coworkers treated (33) 1,1'-dimethylferrocene with n-amylsodium and obtained, after carbonation, a 52% yield of a dimethylferrocenedicarboxylic acid. The structure of this acid was not established. Benkeser and coworkers reported (34) that treatment of methyl, ethyl, isopropyl, and t-butylferrocenes with n-amylsodium or n-amylpotassium in 1:1 mole ratio results in dimetalation and monometalation in a ratio of about 4:1. In all cases, the monometalation products consisted of mixtures of 3 and 1' metalloalkylferrocenes in 1:2.6 ratio. A statistical distribution would be a 1:2.5 ratio. The dimetalation products were 2-alkyl-1,1'-dimetalloferrocene and 3-alkyl-1,1'-dimetalloferrocene and 3-alkyl-1,1'-dimetalloferrocene. The amount of 3-alkyl derivatives was greatest in all cases and its predominance increased as the size of the alkyl substituent increased. No α-substitution was found in any of these reactions. In this study, analysis of the reaction mixture was by vapor phase chromatography of the reaction products of the organometallic compounds with trimethylchlorosilane and with triethylbromosilane. The monometalation products were identified by comparison of the retention times of the silane derivatives with authentic samples. The silane derivatives of the dimetalated species were isolated by v.p.c. and identified by n.m.r. spectroscopy.

Furan is dimetalated (35) in the 2- and 5-positions by n-amylsodium. The metalation (22) of thiophene is similar. Anisole has been metalated with n-amylsodium (36) and n-butylsodium (37). Substitution occurred in the ortho position. Ortho substitution is also observed (37) when N, N-dimethylaniline is treated with n-amylsodium and when diphenyl sulfide is treated with phenylsodium. The structures of the products were established in all of the above reactions by carbonation and identification of the resulting acids. The ether and amino groups enhance (37) the reaction which is in accord (3, 38) with the expected increase in acidity due to the inductive effect.

Roberts and coworkers have studied (38) the homogeneous exchange reactions of deuterated benzene derivatives with potassium amide in ammonia. With electron attracting substituents it was found that exchange rates were ortho > meta > para. This is the order one would expect for the acidity of the hydrogens at these positions due to the inductive effect of the substituents. Puterbaugh and Hauser reported (39) the ortho metalation of benzyldimethylamine V followed by isomerization to the side chain derivative VII. The reaction was followed by treating the metalation mixture with excess benzophenone. The amino alcohols VIII and IX which formed from VI and VII were isolated and identified by comparison with authentic samples. The ortho substitution of these compounds is postulated (39) to result from coordination of the metal of the reagent by the free electrons of the heteroatom, which places the reagent in a position close to the ortho position of the ring. Inductive effects also favor ortho substitution in these cases (38).



The most satisfactory mechanism for metalations by alkylsodium and alkylpotassium is protophilic substitution. None of the available data contradicts this mechanism, but the arguments excluding other possible mechanisms are in many cases based on meager evidence.

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STRUCTURE OF CYCLOPROPANE

Reported by Virgil Weiss   October 5, 1964

INTRODUCTION

The fact that cyclopropane possesses characteristics similar to olefins has been verified from spectra[1], dipole moments[2], and reactions[3]. Several theoretical attempts have been made to correlate these phenomena with the structure of cyclopropane. This review will present these ideas and their consequences.

THEORY OF THE STRUCTURE

Duffey[4], using a nontetrahedral carbon atom, was one of the first to consider the bonding in cyclopropane. Assuming that the radial parts of the 2s, $2p_x$, $2p_y$, $2p_z$ functions were so similar that their differences were negligible, he used a linear combination of the angular parts to approximate each of the bond forming orbitals on a carbon. The functions had the form

$$f_i = a_i s + b_i p_x + c_i p_y + d_i p_z \qquad (1)$$

where i is 1,2,3, or 4. By requiring the four **hybridized atomic** orbitals on any one carbon atom to be orthonormal, the coefficients a_i, b_i, c_i, d_i were determined. Since any carbon in cyclopropane has two sets of equivalent orbitals, he chose one of these sets of equivalent orbitals and related the direction of the maximum of one of the orbitals in this set to a coefficient, for example a_j, of the second orbital in this set. Then choosing the polar angle ϕ to equal 180° such that $p_y = o$ and $p_x = \sqrt{3}\sin\theta$, he maximized one of the orbitals with respect to the other polar angle θ. Duffey found the angle between the orbital maxima equaled $90^o + \theta$ where

$$\tan\theta = a_j{}^2/(1 - 2a_j{}^2)^{\frac{1}{2}} \qquad (2)$$

Using Pauling's[5] criteria of maximum overlap and choosing the angle between the orbitals used to form the two C-C bonds as small as possible, i.e, 90°, he calculated on H-C-H angle of 180°.

Kilpatrick and Spitzer[6] employed the same type of orbitals as Duffey, but did not put any restrictions on any of the valence angles. They let f_1 and f_2 be the orbitals used to form the two C-C bonds and f_3 and f_4 be the orbitals used to form the C-H bonds. Letting the xz plane contain the f_1 and f_2 orbitals and the yz plane contain the f_3 and f_4 orbitals, and applying the conditions of orthonormality, they obtained the following orbitals.

$$f_1 = as + bp_z + (1/2)^{1/2}p_x \qquad (3)$$

$$f_2 = as + bp_z - (1/2)^{1/2}p_x \qquad (4)$$

$$f_3 = bs - ap_z + (1/2)^{1/2}p_y \qquad (5)$$

$$f_4 = bs - ap_z - (1/2)^{1/2}p_y \qquad (6)$$

$$\text{where } b = (1/2 - a^2)^{1/2} \qquad (7)$$

They assumed that in "strained" compounds the maxima of hybrid orbitals do not necessarily coincide with the direction of the bonds. Instead, they proposed that the bond strength is proportional to the value of the orbitals in the direction necessary to form a bond. When the axis of the bond orbital and the internuclear axis coincide then the maximum bond strength is obtained. Using this idea they maximized f_1 with respect to a and expressed the result in terms of θ_0, the angle between the z axis and the axis of f_1. Employing equation (7) they found that

$$a = \left(\frac{1}{2 + 6\cos^2\theta_0}\right)^{1/2} \qquad (8) \qquad\qquad b = \left(\frac{3\cos^2\theta_0}{2 + 6\cos^2\theta_0}\right)^{1/2} \qquad (9)$$

Therefore θ_{34}, the angle between the bonds formed with the orbitals f_3 and f_4, is given by the expression

$$\tan\theta_{34} = -\frac{2\,(1 + 3\cos^2\theta_0)^{1/2}}{3\cos^2\theta_0} \qquad (10)$$

Using different values for the C-C-C bond angle, $2\theta_0$, they calculated the H-C-H angle, θ_{34}, and the corresponding C-C and C-H bond strengths. Their results are tabulated in Table 1.

TABLE 1

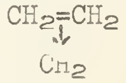
C-C and C-H bond strengths and H-C-H bond angle as a function of C-C-C bond angle.

C-C-C bond angle	C-C bond strength	H-C-H bond angle	C-H bond strength
0°	1.414	126°52'	1.982
60°	1.887	121°58'	1.989
90°	1.984	115°23'	1.995
108°	2.000	109°58'	2.000
109°28'	2.000	109°58'	2.000
120°	1.996	105°50'	1.998
180°	1.932	90°	1.732

Kilpatrick and Spitzer, assuming that the bond energies were proportional to the square of the bond strengths, obtained a strain energy of 8 kcal per CH_2 group [6,7].

Dunitz and Schomaker[7] made calculations similar to Kilpatrick and Spitzer except both the C-C and C-H bonds were considered in obtaining the best energy. They obtained a value of 7.0 kcal per CH_2 group. The observed strain is 9.2 kcal per CH_2 group[30].

To account for the unsaturated characteristics of cyclopropane, Walsh[8] introduced the unsymmetrical π complex formula for cyclopropane instead of the conventional cyclic one. In this form, two of the carbon atoms would be trigonal and the third in a tetrahedral state. Cyclopropane would then have a disturbed ethylene structure where two of the electrons of the ethylene bond form bonds with three carbon atoms:



$$\underset{\underset{CH_2}{\downarrow}}{CH_2{=}CH_2}$$

Robinson[9], while criticizing Walsh's formula because it did not reflect the symmetry of an equilateral triangle, preferred to explain peculiarities of cyclopropane by the application of quantum mechanical principles on the conventional molecular structure. He did not however make any calculations for cyclopropane at this time. In a second paper, Robinson[10] suggested that the carbon atoms were not trigonal, but strained tetrahedral.

In a criticism of Walsh's work, Mc Dowell[11] suggested that the olefinic character should be observed in the Raman spectrum of the molecule. However, absorption in the 1600 cm^{-1} region, a characteristic of the double bond in ethylene is not observed.

In a rebuttal to these criticisms Walsh[12] stated that the symmetry is retained if three equivalent resonance forms are considered. Also, one could not expect cyclopropane to possess properties of ethylene because the structure is so greatly upset. Later Walsh[13] stated that his proposed structure was just his way of expressing the fact that cyclopropane possessed a large amount of olefinic character.

Through the use of electron diffraction[14,15], it was established that cyclopropane was a symmetrical ring with the three carbon atoms at the vertices of an equilaterial triangle. The C-C bond length was $1.54\ A^\circ \pm .03$ and the C-H bond length was $1.08\ A^\circ \pm .03$. The H-C-H angle was $118.2^\circ \pm 2^\circ$ and the H-C-H plane was perpendicular to the carbon atom plane. Thus it was established that the H-C-H angle was closer to being trigonal than tetrahedral.

This conclusion was in an agreement with a dipole moment measurement and calculations of the force constants of the C-C and C-H bonds in cyclopropane. Rogers and Roberts[2] showed that the dipole moment of cyclopropyl chloride was 0.3D lower than that for isopropyl chloride and cyclopentyl chloride. They interpreted this to mean that the carbon atom in cyclopropyl chloride must be more electronegative than in the other two compounds. Since a sp^2 hybridized carbon atom is more negative then one of sp^3 hybridization, they concluded that the hybridization in cyclopropyl chloride must be nearer sp^2 than sp^3.

Assuming that the hydrogen atoms are located at tetrahedral angles outside the ring plane, Saksena[16] calculated a C-C stretching force constant of 4.04×10^5 dynes

cm^{-1} thus indicating a weaker bond in cyclopropane than ethane. Using infra-red and Raman spectra for his calculations, Linnett[17] calculated a C-H stretching force constant of 5.05×10^5 dynes cm^{-1}. The stretching force constant of the C-H bond in ethylene is 5.1×10^5 dynes cm^{-1} [18], and that of the methylene groups in paraffins is 4.6×10^5 dynes cm^{-1} [19], thereby indicating that the hybridization of the carbons in cyclopropane is nearer sp^2 than sp^3.

Sugden[20] applied the theory of non-localized molecular orbitals to the problem of determining the structure of cyclopropane. The fundamental point of this theory is that any molecular orbital, which may be bonding or otherwise in all the nuclei, must conform to an irreducible representation of the point group of the nuclear skeleton, in our case D_3h. Mulliken[37] had shown that for the D_3h point group it was possible to construct three molecular orbitals with the following eigenfunctions:

$$\phi_1 = 1/\sqrt{3}(\psi_1 + \psi_2 + \psi_3) \qquad (11)$$
$$\phi_2 = 1/\sqrt{2}(\psi_1 - \psi_2) \qquad (12)$$
$$\phi_3 = 1/\sqrt{6}(\psi_1 + \psi_2 - 2\psi_3) \qquad (13)$$

where ψ_1, ψ_2, and ψ_3 are atomic orbitals on carbons 1,2, and 3 respectively, and where ϕ_2 and ϕ_3 are doubly degenerate.

Sugden used linear combinations of H1s and C2s, $2p_x$, p_y, p_z atomic orbitals to construct the orbitals of the CH_2 group. These CH_2 orbitals were then used to construct $(CH_2)_3$ molecular orbitals. Superimposing the three sets of molecular orbitals upon one another, the electron distribution has the general shape as shown in Figure 1.

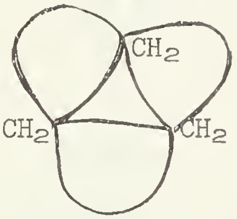


Figure 1

In 1949, two fundamental studies of cyclopropane appeared. The first of these was by Walsh[21], and developed his previously proposed idea that the CH_2 groups in cyclopropane were similar to those in ethylene. As in ethylene, each carbon atom was formed from three sp^2 hybrid orbitals which were in one plane and a pure p orbital which had its symmetry axis perpendicular to this plane. As shown in Figure 2, the molecular orbitals were formed by the overlap of the 2p orbitals whose symmetry axis lay in the C-C-C plane as well as one sp^2 orbital which was also in the C-C-C plane. The other two sp^2 orbitals were in a plane perpendicular to the C-C-C plane and were used to bond the two hydrogens.

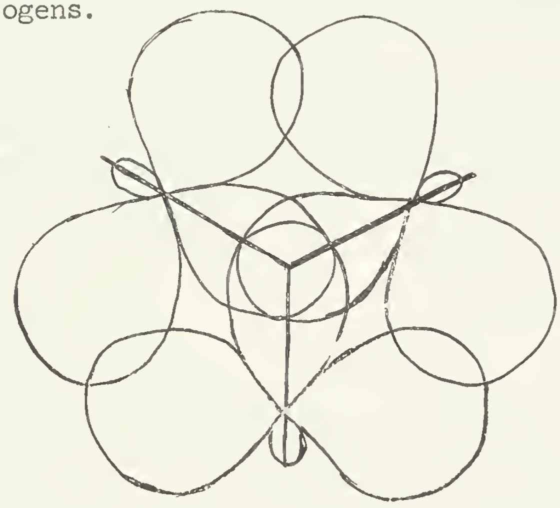


Figure 2

Assuming that the C-H orbitals were localized but the molecular orbitals - ϕ_1, ϕ_2, ϕ_3 - which were formed by the overlapping of the corresponding atomic orbitals - ψ_1,

ψ_2, ψ_3 - of each carbon were non localized, then according to Mulliken, the molecular orbitals were given by the same equations as used by Sugden[20] - equations (11), (12), and (13).

As can be seen in Figure 2 there were two types of overlapping atomic orbitals. Those composed of pure p orbitals and those composed of sp^2 hybrids. Letting ϕ_1, ϕ_2, ϕ_3, represent the molecular orbitals formed from the sp^2 hybrids, then ϕ_1 will be the bonding orbital and ϕ_2 and ϕ_3 the antibonding orbitals.

Letting $\overline{\phi}_1$, $\overline{\phi}_2$, $\overline{\phi}_3$ represent the molecular orbitals formed from pure p orbitals, then $\overline{\phi}_2$ and $\overline{\phi}_3$ were bonding and $\overline{\phi}_1$ was antibonding. Assuming that the bonding orbitals in each of the sets were lower in energy than the antibonding orbitals in the other set, four electrons were put in $\overline{\phi}_2$ and $\overline{\phi}_3$, and two in $\overline{\phi}_1$. Their probability pattern is given in Figure 3, where a represents the two electrons in $\overline{\phi}_1$ and b,d,e represent the four electrons in $\overline{\phi}_2$ and $\overline{\phi}_3$. Areas b,d,e, were the same as those predicted by Sugden[20].

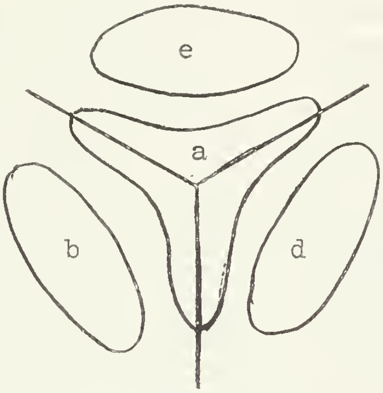


Figure 3

Walsh emphasized the fact that although he assumed non-localized orbitals in the ring, there can be some localized bond character and that the overlap between any pair of 2p orbitals is intermediate between the overlap of a π bond and a σ bond.

Using the same type of hybridization, the stability and structure of spiropentane was explained. In considering spiropentane, only the central carbon atom needed to change hybridization; the other atoms had the same type of orbitals as in cyclopropane. If the central carbon atom formed an sp orbital with one lobe of that orbital directed to the center of each ring and also had two pure p orbitals perpendicular to the sp orbital and to themselves, then each ring had the same type of molecular orbitals as a cyclopropane ring. Since spiropentane exists[22] and the rings are at 90° [23], his ideas are somewhat substantiated. If the hybridization of the central carbon in spiropentane is imposed on two of the carbons in a single cyclopropane ring, then a true π bond should be formed. And, therefore, cyclopropane compounds should be feasible. Compounds of this type have indeed been made[24,25].

The other major work at this time was a valence bond calculation by Coulson and Moffitt[26]. Their presentation was an elaboration of the ideas proposed by Kilpatrick and Spitzer[6] regarding compounds with non-tetrahedral carbon atoms. They used Dirac's equation for the pertubation energy of bonding which is the energy obtained upon bringing together electrons in orbitals ψ_i. This equation in its most general form is

$$E = \text{constant} - 1/2 \sum_i \sum_{j>i} (1 + 4\,\overline{S_i \cdot S_j}) \cdot J_{ij}$$
$$\text{where } J_{ij} = \int \psi_i^*(1)\ \psi_j(2)\ H\ \psi_j^*(1)\ \psi_i(2)\ d\tau_1\, d\tau_2 \qquad (14)$$

and $\overline{S_i \cdot S_j}$ are the eigenvalues of scalar product operators representing the relative orientations of the spin vectors of the electrons associated with the orbitals ψ_i, ψ_j. This formula is valid if the lack of orthogonality between the normalized ψ_i and higher exchange intergrals is neglected. Coulson and Moffitt then applied the approximation of perfect pairing. This made $\overline{S_i \cdot S_j} = -3/4$ for the electrons that are fully coupled and $\overline{S_i} \cdot S_j = 0$ for the non bonding electrons.

The energy then becomes

$$E = \text{constant} - 1/2 \sum_{i} \sum_{j>i} J_{ij} + 3/2 \sum_{\text{bonds}} J_{aa'} \qquad (15)$$

where ψ_a and $\psi_{a'}$ are the bonded pairs of orbitals on atoms A and A'. In order to increase the amount of overlap between orbitals on different atoms, they constructed hybridized orbitals from linear combinations of $C2s$, $2p_x$, $2p_y$, $2p_z$ atomic orbitals just as Kilpatrick and Spitzer had done. Using the conditions of orthonormality they expressed the energy as a function of the hybridization ratios of both the C-C and C-H bonds. They minimized the energy with respect to both of the hybridization ratios since the C-C-C angles differs from the H-C-H angle and, therefore, the hybridization ratios in the respective bonds should differ. Assuming the C-H bond was straight, i.e., neglecting the H-H repulsions, they calculated an H-C-H angle of 116° and an angle of 104° for the two orbitals that are used to bond the other two carbons. Therefore, the C-C internuclear axis and the symmetry axis of one of the lobes used to form the C-C bond differed by 22°. The authors described these bonds as bent and state that it is for this configuration that cyclopropane is in its lowest energy state.

The two most important factors neglected in this treatment were neglect of the H-H repulsion which would tend to open the H-C-H angle, and the restriction to a pure valence state model in which any resonance energy other than that implied in the choice of the best possible hybrid was neglected. The approximation that the radial parts of the wave functions were so similar their differences could be neglected was also made.

In comparing the hybridization ratios of cyclopropane with those of an unstrained tetrahedral atom, the C-C bonds of cyclopropane possess more p character which is in the C-C-C plane while the C-H bonds have less p character. This can be seen in Table 2. The C-C hybridization parameter is λ and the C-H hybridization parameter is μ. The larger the value of the hybridization parameter the greater the amount of p character in the bond. The difference between the internuclear C-C axis and one of the orbitals used to form the C-C bond is θ.

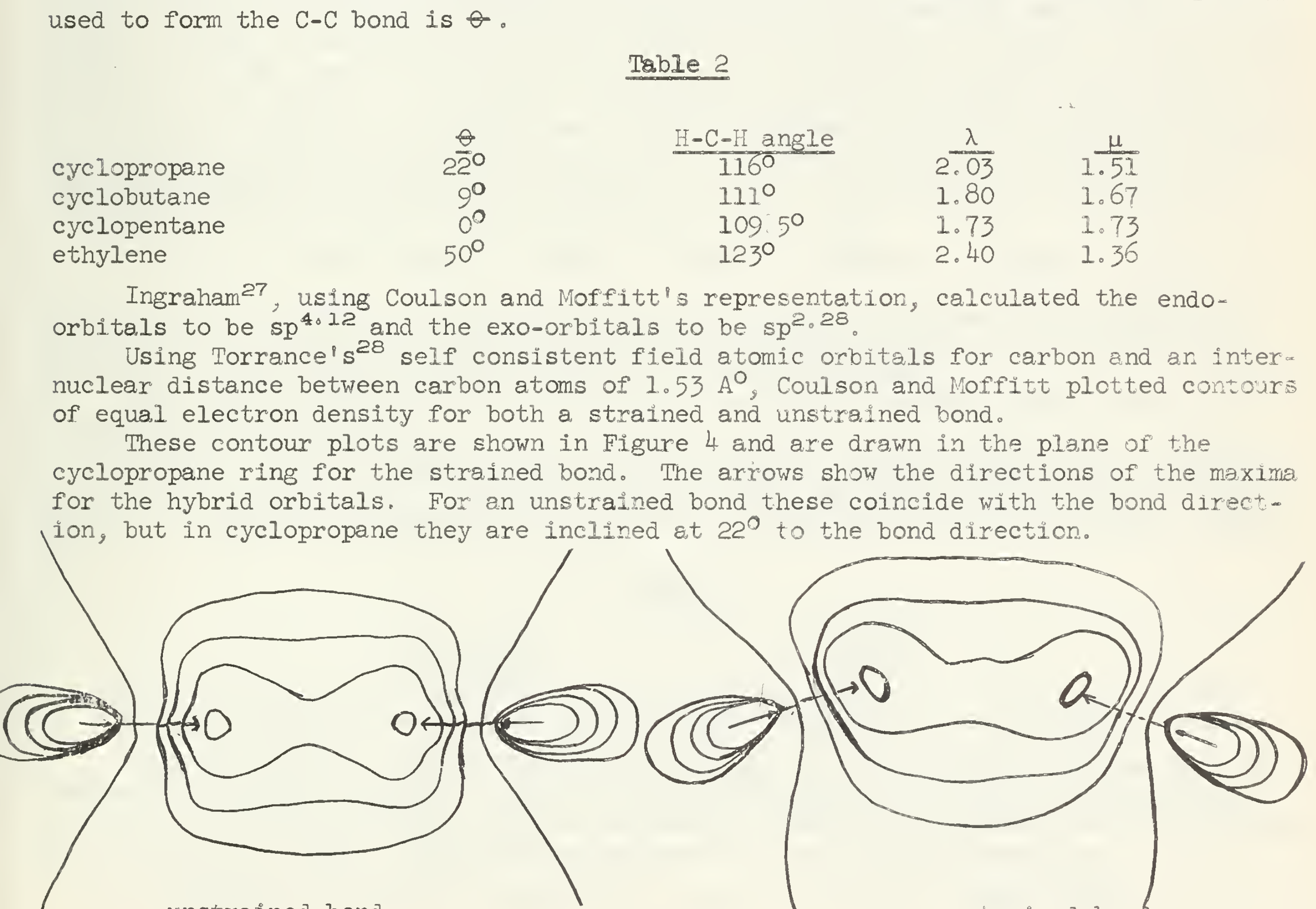
Table 2

	θ	H-C-H angle	λ	μ
cyclopropane	22°	116°	2.03	1.51
cyclobutane	9°	111°	1.80	1.67
cyclopentane	0°	109.5°	1.73	1.73
ethylene	50°	123°	2.40	1.36

Ingraham[27], using Coulson and Moffitt's representation, calculated the endo-orbitals to be $sp^{4.12}$ and the exo-orbitals to be $sp^{2.28}$.

Using Torrance's[28] self consistent field atomic orbitals for carbon and an internuclear distance between carbon atoms of 1.53 A°, Coulson and Moffitt plotted contours of equal electron density for both a strained and unstrained bond.

These contour plots are shown in Figure 4 and are drawn in the plane of the cyclopropane ring for the strained bond. The arrows show the directions of the maxima for the hybrid orbitals. For an unstrained bond these coincide with the bond direction, but in cyclopropane they are inclined at 22° to the bond direction.



unstrained bond

strained bond

Figure 4

In the total electron density diagram for all six bonding electrons, there was considerable charge in the middle of the triangle formed by the carbon atoms. This was in agreement with Walsh's probability plot.

Coulson and Moffitt also calculated the energy using contributions from the combination of all possible valence states. The difference between this energy and that for only the perfect pairing approximation should be the energy due to resonance (i.e., a delocalization of electrons). They calculated this energy to be about 1 e.v. per CH_2 group. The strain energy was also calculated. This was the difference in energy between the unstrained CH_2 group, such as in gaseous polyethylene, and the best energy obtained for cyclopropane by minimization. Allowing for small contributions of σ-π type C-C bonding and the resonance energy, they calculated the strain energy to be about 1/2 to 1 e.v. per CH_2.

However, Weltner[29] has pointed out that one of Coulson and Moffitt's exchange integrals was wrong and that the calculated resonance energy should be 0.0 e.v. Therefore, the calculated strain energy would be about 1 1/2 to 2 e.v. per CH_2. The strain energy obtained from heat of combustion data is about 0.40 e.v. per CH_2[30].

Later Handler and Anderson[31] suggested using non orthogonal atomic orbitals to construct molecular orbitals. Using linear combinations of C2s, $2p_x$, p_y, p_z atomic orbitals, they constructed hybridized atomic orbitals on the carbon such that the orbitals used to bond to the other two carbons were not orthogonal, but instead had maximum bond forming power in the Pauling sense. The other two hybridized atomic orbitals used to form the C-H bond were required to be orthogonal to themselves and to the first two atomic orbitals used to bond the other carbons. Using these conditions they calculated an H-C-H angle of 122° and obtained an energy of $6Q + 8.8\beta$ as compared to an energy of $6Q' + 6\beta'$ using all orthogonal hybridized atomic orbitals on a carbon.

Coulson and Goodwin[32] proposed using the principle of maximum overlap for all bonds to determine the bond angles in cyclopropane. They used the same atomic orbital wave functions as Kilpatrick and Spitzer where ψ_{ij} represented an atomic orbital with origin on C_i and used to bond C_i and C_j. The wave function ψ_{ij} was then resolved into two parts, one parallel to the C_iC_j internuclear axis and the other perpendicular to it. The part parallel to the axis was used to form the σ part of the bond and the perpendicular part was used to form the π part. The overlap integral between C_i and C_j was then expressed as a sum of two parts, one due to σ bonding and the second due to π bonding. The expression had the following form:

$$S_{ij} = S_{ij\sigma} + S_{ij\pi} = \int\psi_{ij\sigma} \cdot \psi_{ji\sigma}d\tau + \int\psi_{ij\pi} \cdot \psi_{ji\pi}d\tau \qquad (16)$$

where S_{ij} is the total overlap between C_i and C_j, $\psi_{ij\sigma}$ is the part of the ψ_{ij} wave function that is parallel to the C_iC_j internuclear axis and $\psi_{ij\pi}$ is the part of the ψ_{ij} wave function perpendicular to the C_iC_j internuclear axis.

They assumed that the C-H bonds were not bent and, therefore, should not be decomposed into two parts.

All the overlap integrals were related through a common constant, a. The total overlap of the molecule, S, was then obtained by adding together the overlap integrals for all the bonds in cyclopropane. The total overlap was then maximized with respect to a. The results are given in Table 3.

Table 3

H-C-H angle	117°48'
C-C-C angle	102°52'
total overlap of the molecule using calculated angles	6.0410
total overlap of the molecule using perfect tetrahedral hybridization	6.0011

Peters[33] suggested making a molecular orbital calculation which employs some of Coulson and Moffitt's ideas. Using a linear combination of 2s and 2p Slater atomic orbitals he constructed three equivalent localized orthogonal bonding molecular orbitals for the C-C bonds which could be expressed by the following equation.

$$\mu ab = N[h(2S_a) + (1-h^2)^{1/2}\{2p\sigma' a(b)\} + h(2S_\sigma) + (1-h^2)^{1/2}\{2p\sigma'_b(a)\}]$$

where a and b represent the atoms forming the molecular orbital, h^2 is the hybridization parameter, N is a normality constant, and 2p $\sigma_a(b)$ denotes a linear combination of $2p_x$, p_y, p_z atomic orbitals on atom a pointing in the general direction of atom b. The atomic orbital does not in general have its angular maximum along the ab internuclear line. He let α be the angle between the C-C internuclear axis and the axis of the hybrid orbital used to form the molecular orbital, i.e., the amount the bond is bent. Using the orthogonality condition between adjacent C-C bonds, h^2 was related to α. By choosing different C-C internuclear distances and C-C-C internuclear bond angles, a graph of $h^2 = f(\alpha)$ was obtained.

For a C-C internuclear distance of 1.54A° and a C-C-C internuclear angle of 60° as was determined by the geometry of the molecule, α was obtained to be at least 21°. An upper limit of 25° was chosen since this would give a tetrahedral angle between the two hybrid atomic orbitals used to bond the other two carbons. The amount of 2s character in the hybrid atomic orbitals was then between 0 and 4 % as compared to 13 %s character for an unstrained system using this same method. Coulson and Moffitt[26] obtained 20 % s character for cyclopropane in their valence bond calculation as compared to 25 % s character using valence bond theory on an unstrained system. An attempt to apply this procedure to the C-H bonds was not as fruitful because the C-H bond distance was not definitely known and orthogonality conditions on the hybrid orbitals lead to an unusable equation because its numerical results were very sensitive to small differences in the assumed geometry of the molecule. The most that could be said was that if the C-H bonds were assumed straight they have about the same amount of s character as is found in the C-H bonds in ethylene.

DelRe[34] has proposed using the MO-LCAO method to obtain the "best" hybrid orbitals. Using carbon atoms composed of orthonormal atomic orbitals, this method then required that the whole overlap matrix between eight orbitals of two atoms forming bonds be brought as close as possible to a form where only one off-diagonal element is non vanishing. This essentially requires that the orbitals which form a bond overlap as much as possible as is consistent with the orthonormality conditions.

In order to use this procedure, two assumptions had to be made: 1) the binding atomic orbitals were all described by the same coulomb integrals, possibly with the exception of π orbitals; 2) the bond integrals between any two atomic orbitals are proportional to the corresponding overlap integrals through a constant which may depend upon the particular pair of atoms under consideration.

Since all four equally hybridized atomic orbitals on a carbon have the same energy before bonding, assumption 1 can be made. Assumption 2 is just the Mullikan[35] approximation.

Veillard and Del Re[36] applied this idea to cyclopropane and obtained an H-C-H angle of about 119° and an angle between the internuclear C-C axis and the hybrid orbital axis of about 22°.

Everyone has assumed that the C-H bond is straight. This assumption is substanitated somewhat in that Flygare, Narath, and Gwinn[37], in a microwave study on 1,1 dichlorocyclopropane, found the C-Cl internuclear axis and the orientation of the quadrupole coupling constant tensor to coincide within experimental error, 15 minutes of arc.

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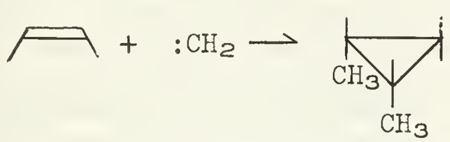
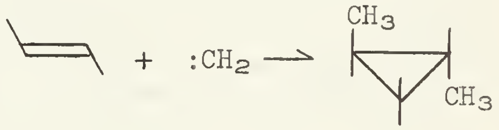
VINYLIDENES AND VINYLIDENECARBENES

Reported by Joseph C. Catlin October 8, 1964

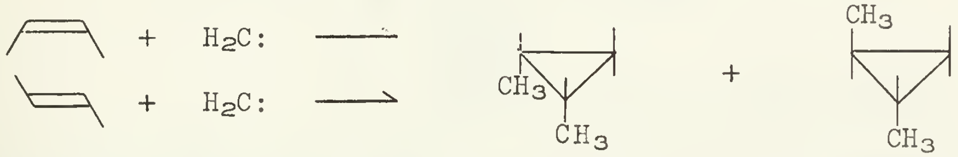
Carbon monoxide ($O{=}C:$) is a stable divalent carbon species. Isocyanides ($R\text{-}\ddot{N}{=}C: \leftrightarrow R\text{-}N^{\oplus}\equiv C^{\ominus}$) form a class of fairly stable compounds containing divalent carbon (1). Both the above examples contain a hetero atom double bonded to the divalent carbon. In this seminar we shall be interested in species containing a divalent carbon double bonded to a second carbon. We will consider both vinylidenes, $R'(R)C{=}C:$, and vinylidenecarbenes, $R'(R)C{=}C{=}C:$.

Before considering vinylidenes and vinylidenecarbenes we will first review some pertinent information concerning carbenes. A carbene can either be in a singlet state, i.e., have all electrons paired, or in a triplet state, i.e., have two unpaired electrons. It has been suggested that in the singlet state the divalent carbon species be called a carbene and in the triplet state a methylene (2). In this seminar we will use carbene and methylene interchangeably. Singlet carbenes add stereospecifically to olefins (3), (4a), (4b).

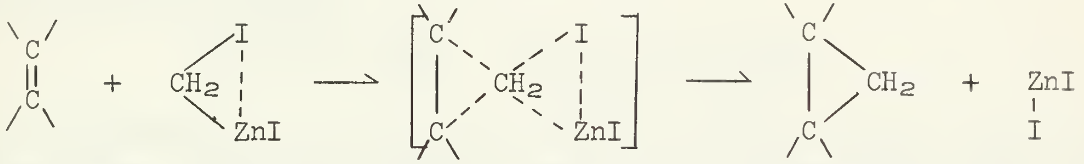




Triplet carbenes add nonstereospecifically to olefins, they act as diradicals (2), (4b).



The reaction of an intermediate species with an olefin to form a cyclopropane ring cannot be regarded as proof of a divalent carbon intermediate. Methylene iodide (5), (6) reacts with a zinc-copper couple to form a zinc methylene iodide complex which adds to an olefin forming a cyclopropane ring.



Kinetic studies can be very helpful in determining if a divalent carbon intermediate participates in a reaction (7a), (7b). Deuterium exchange of chloroform is rapid compared to the hydrolysis, which is first order in both chloroform and base. The following mechanism has been proposed for the hydrolysis of chloroform:

$$CHCl_3 \underset{OH}{\overset{fast}{\rightleftharpoons}} CCl_3^{\ominus} + H^{\oplus}$$

$$CCl_3^{\ominus} \xrightarrow[slow]{} Cl^{\ominus} + :CCl_2$$

$$:CCl_2 \xrightarrow[OH^{\ominus},H_2O]{fast} CO + HCO_2^{\ominus}$$

In 1894, P. Fritsch (8), W.P. Buttenberg (9) and H. Wiechell (10) observed that upon heating diphenylmonochloroethene to 180°-200° in a sodium ethoxide solution, the following reaction took place:

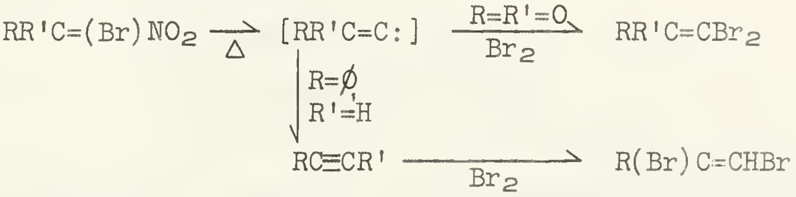
$$(C_6H_5)_2C{=}CHCl \xrightarrow{Base} C_6H_5C{\equiv}CC_6H_5$$

A possible mechanism for the above reaction could be one involving α-elimination and the formation of a vinylidene intermediate which rearranged to form tolan.

$$(C_6H_5)_2C{=}CHCl \longrightarrow [(C_6H_5)_2C{=}C:] \longrightarrow C_6H_5C{\equiv}CC_6H_5$$

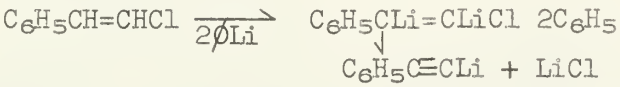
The scope and usefulness of the reaction of diarylchloroethenes with base to form disubstituted acetylenes has been greatly broadened by using potassium amide for the base and carrying the reaction out in liquid ammonia. Coleman and coworkers (11),(12) studied the reactions of chloroethenes with potassium amide in liquid ammonia. They found that it took only a short time for diphenylchloroethene to be converted to tolan under these conditions, compared to Buttenberg's 8 hours at 180°-200° using sodium ethoxide and ethyl alcohol. They studied ortho, meta, and para substituted diarylbromoethenes and diarylchloroethenes. In all cases, the symmetrical tolans were formed. The authors suggested that a halide ion is first lost, leaving a cation which is stabilized by the migration of an aryl group and the electron bonding it to the ethene. The electron deficiency is then satisfied by loss of a proton and formation of a triple bond.

1,1-Diphenyl-2,2-dihaloethenes react with base to form phenylacetylene (11), (13), (18). This reaction may proceed by the same mechanism as followed for 1,1-diphenyl-2-haloethenes. Allen and Wilson (14) studied the pyrolysis of certain bromonitro compounds. When β-bromo-β-nitrostyrene is heated to decomposition α,β-dibromostyrene can be isolated. From the pyrolysis of 1,1-diphenyl-2-bromo-2-nitroethene they isolated 1,1-diphenyl-2,2-dibromoethene. Allen and Wilson proposed the following mechanism for the reactions they observed:



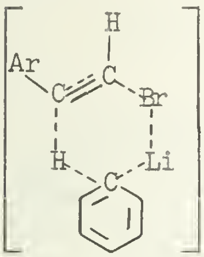
$$\begin{array}{lll} RR'C{=}(Br)NO_2 \xrightarrow[\Delta]{} [RR'C{=}C:] & \xrightarrow[Br_2]{R=R'=O} & RR'C{=}CBr_2 \\ \qquad\qquad\quad \big\downarrow {\scriptstyle R=\phi,\ R'=H} & & \\ \qquad\qquad\quad RC{\equiv}CR' & \xrightarrow[Br_2]{} & R(Br)C{=}CHBr \end{array}$$

Gilman and coworkers (15) found that in ethyl ether β-bromostyrene reacts with butyllithium to form phenylacetylene. Wittig and coworkers (16) studied the kinetics of the reaction of β-chlorostyrene with phenyllithium and found it to be third order, first order in β-chlorostyrene and second order in phenyllithium. On this basis they proposed the following mechanism:



$$\begin{array}{l} C_6H_5CH{=}CHCl \xrightarrow[2\phi Li]{} C_6H_5CLi{=}CLiCl\ 2C_6H_5 \\ \qquad\qquad\qquad\qquad\quad \downarrow \\ \qquad\qquad\qquad\qquad\quad C_6H_5C{\equiv}CLi + LiCl \end{array}$$

Cristol and Helmreich (17a) studied the kinetics of the reaction of cis- and trans-β-bromostyrene. Contrary to Wittig's results, they found the reaction to be first order in β-bromostyrene and first order in phenyllithium. Cristol and Helmreich eliminated the possibility of a cyclic transition state, I, on the basis of the similar magnitude of the rates of reaction of the cis and trans isomers (cis β-bromostyrene reacts with sodium hydroxide in 2-propanol 200,000 times as fast as the trans isomer) (17b), and one would not expect the cis isomer to form a cyclic transition state similar to that which could exist for the trans isomer. As evidence for an α-elimination, in addition to the similar magnitude of reactivity of the cis and trans-2-bromostyrene, the authors refer to work of Wittig's (16) in which it was shown that β-chloro-β-methylstyrene reacts very slowly with phenyllithium. If the reaction were a β-elimination one would expect β-chloro-β-methylstyrene to react faster than β-chlorostyrene. However, it is interesting to note that Curtin and coworkers (18) have reported that β-chloro-α-methylstyrene is also less reactive than β-chlorostyrene.



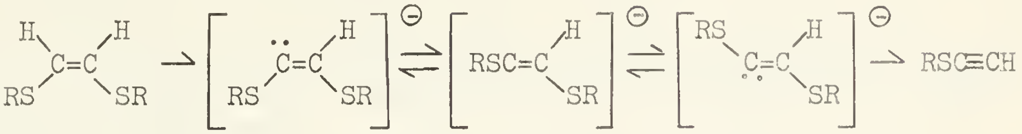
I

Parham and coworkers (20), (21) observed the following reaction of Bis (substituted-mercapto) ethenes with n-butyllithium, and Curtin and Murdoch (22) reported a similar reaction using sodium or potassium acetylide as the base:

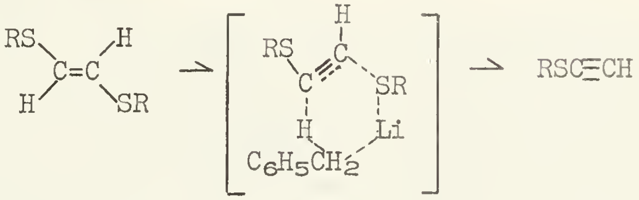
$$C_6H_5SCH{=}C(H)SC_6H_5 \longrightarrow C_6H_5SC{\equiv}CH{+}C_6H_5SLi$$

Parham and coworkers proposed three possible mechanisms: β-elimination, cyclic, and α-elimination. The proposed mechanisms were as follows:

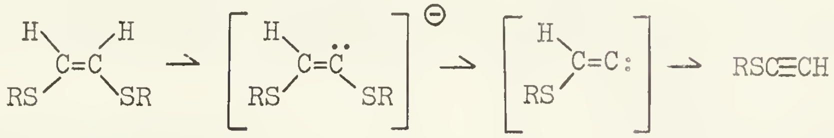
β-elimination



cyclic elimination



α-elimination



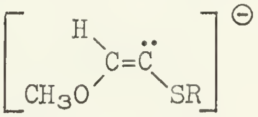
The authors felt that they were able to eliminate the possibility of α-elimination because sulfur increases the acidity of an α-hydrogen atom more than oxygen does (23), after consideration of the following reactions:

$$RS\text{-}CH{=}CHSR \longrightarrow RS\text{-}C{\equiv}CH$$

$$RS\text{-}CH{=}CHOCH_3 \longrightarrow RS\text{-}C{\equiv}CH$$

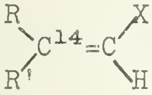
$$EtO\text{-}CH{=}CH\text{-}OEt \longrightarrow \text{No reaction}$$

Therefore, in the reaction of 1-phenythio-2-methoxyethene one would expect the hydrogen α to the phenylthio group to be lost, II. If α-elimination were followed the final product would be a sulfide and not an ether.

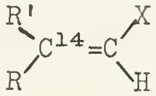


II

Much additional information concerning the possibility of a carbene intermediate in the basic ethene-acetylene rearrangement has been obtained using carbon-14. If the rearrangement goes through a carbene intermediate, III and IV should give the same ratio of V and VI because both III and IV would give the same intermediate carbene.



III

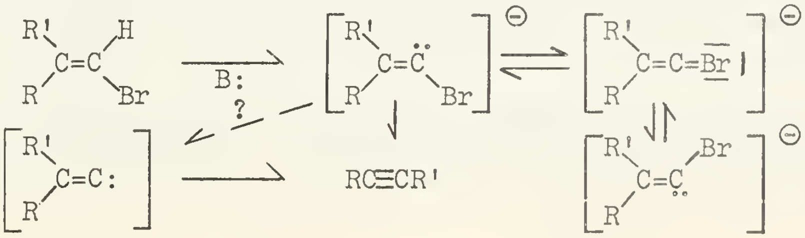


IV

$R'C^{14}\equiv CR$ V

$RC^{14}\equiv CR'$ VI

Bothner-By (24) studied the stereochemistry of the rearrangements of both cis- and trans-1-p-bromophenyl-1-phenyl-2-bromoethene when they reacted with potassium t-butoxide. With each isomer he observed that the aryl group trans to the bromine migrated preferentially. The relative amount of p-bromobenzene that migrates in the above reactions is not important, but as previously stated, if the reaction goes through a carbene intermediate the same ratio of p-bromobenzene to benzene migration must exist in each case because of the symmetry of the carbene intermediate. This information allows us to eliminate the possibility of the major part of the reaction going by a carbene intermediate. Bothner-By has proposed the following mechanism of reaction:

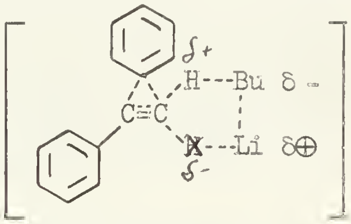


Vinyl carbanions are known to be sterically stable (25).

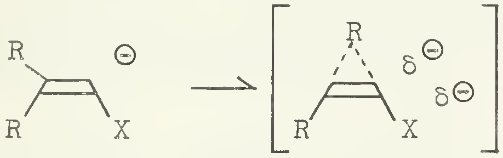
Curtin and coworkers (18), (26) looked at reactions similar to those Bothner-By studied but used BuLi rather than t-BuOK for the base. Their results agreed with those obtained by Bothner-By, predominantly trans migration. Other workers (27) have found that reaction of sodium-2-hydroxyethoxide with both the cis and the trans-isomers of 2-bromo-1-p-methoxyphenyl-1-phenylethene gave p-methoxyphenyl group migration predominantly in both cases.

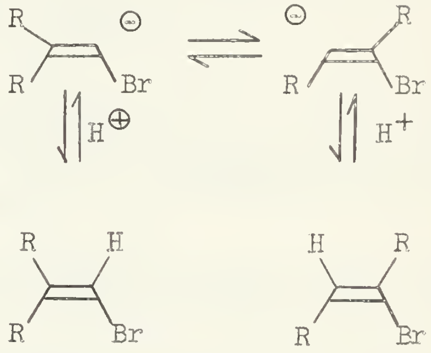
Curtin and coworkers (18), (26) suggested that as an alternate to a carbene intermediate, the ethene-acetylene rearrangement could go through a vinyllithium intermediate, VII. Vinyllithium compounds are known to be sterically stable (28). An attempt was made to intercept VII, R=R'=C_6H_5 as a possible intermediate in the rearrangement of diarylethenes to diarylacetylenes by pouring the reaction mixture over dry ice at about 70% completion (18), (19). Less than 0.5% of the corresponding acid was isolated. The possibility of a concerted reaction with the transition state VIII was then suggested. Cristol and coworkers (29) suggested either a concerted mechanism or one involving either a carbanion or an organolithium compound. Jones and Damico (30) reported that substituents on the trans-aryl group had little effect on the relative rate of rearrangement. They found that a p-methoxy group on the trans-phenyl group accelerated the reaction 2.5 times relative to a p-methoxy group on the cis-phenyl group; p-chlorine trans 0.4 relative to p-chlorine cis. This effect is similar to that observed by P. Beltrame and G. Favinic (31) for formation of disubstituted acetylenes. The above information favors a concerted reaction, IX.

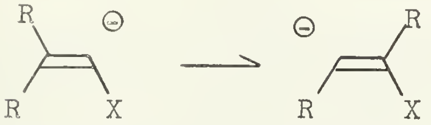
[RR'C=C(Br)Li] VII



VIII

IX


XI


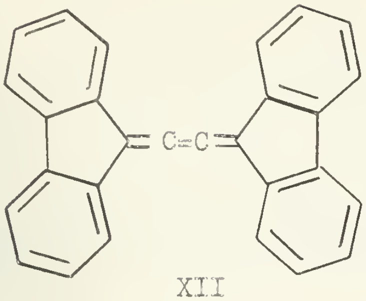
X


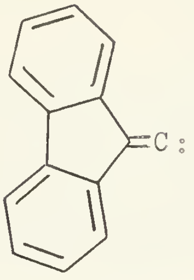
X seems unlikely for two reasons. In mechanism X the migrating group would become electron rich so electron-withdrawing groups would be expected to speed the reaction, but in fact electron-donating groups speed the rate of reaction. Prilchard and Bothner-By (32) found that deuterium exchange took place at one hundred times the rate of the basic hydrolysis. Therefore, one would expect equilibrium XI to exist if mechanism X were followed. No 1-phenyl-2-bromo-2-phenylethene has been isolated from the reaction, further arguing against the possibility of mechanism X.

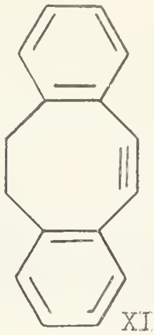
When the aryl groups are free to migrate, a concerted mechanism seems likely. If the aryl groups could not migrate it seems likely that the reaction would go through a divalent carbon intermediate. Hauser and Lednicer (33) observed that 9-bromomethylenefluorene reacted with KNH_2 in NH_3 to give two products: a dimer, (XII), and a nitrogen containing product.

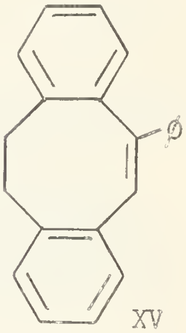
Curtin and coworkers (34a), (34b), (35), (36) studied diarylvinylhalides which were modified to stop rearrangement. They found that the main product of the reaction of 9-bromomethylenefluorene with phenyllithium was the dimer XII. They suggested that

the reaction proceeds through a carbene, XIII. They also observed that 9,10-dihydro-


XII

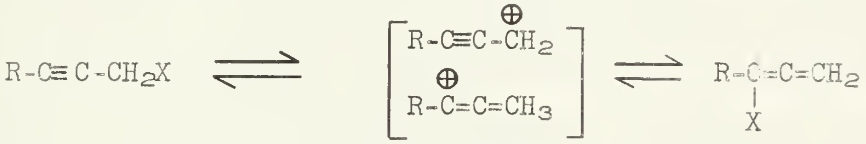

XIII


XIV


XV

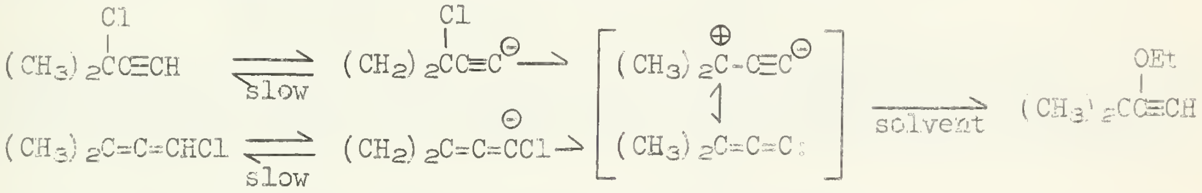
9,9-di-n-propyl-10-chloromethyleneanthracene reacted with phenyllithium to give a 15% yield of dimer. A carbene intermediate was also suggested for this reaction. This carbene was subsequently trapped (34b) with thiophenylate ions (34c) and with several different olefins. 1-chloromethyl-2,3,6,7- Dibenz-2,6-cycloheptadiene reacts with phenyllithium to form a rearranged product containing an eight membered ring, XIV, by the same mechanism as the acyclic rearrangement. Because of ring strain, XIV reacts further to yield XV.

The rearrangement of acetylene to allene, or allene to acetylene, is known as the propargylic rearrangement (37). The mechanism is as follows:



$$R\text{-}C\equiv C\text{-}CH_2X \rightleftharpoons \left[\begin{array}{l} R\text{-}C\equiv C\text{-}\overset{\oplus}{C}H_2 \\ R\text{-}\overset{\oplus}{C}=C=CH_3 \end{array}\right] \rightleftharpoons \underset{\displaystyle X}{R\text{-}C}=C=CH_2$$

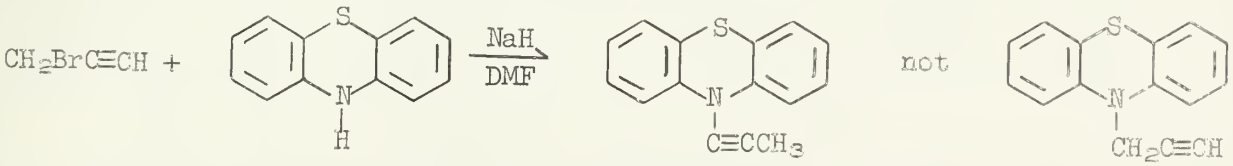
The solvolysis of 3-chloro-3-methyl-1-butyne in acetic acid gives propargylic and allenyl acetate by a first-order process in the presence of acetate ions (38). Hennion and coworkers (39) studied the hydrolysis of 3-chloro-3-methyl-1-butyne, XVI, and 1-chloro-3-methyl-1,2-butadiene, XVII. In 80% ethanol they observed that XVI underwent a first-order reaction while XVII did not react. In sodium hydroxide in 80% ethanol both the diene and the acetylene underwent a second-order reaction. They proposed the following mechanism for the second-order reaction:



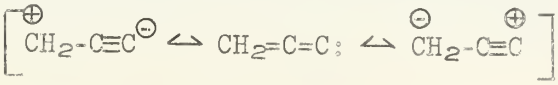
$$\begin{array}{l} (CH_3)_2\overset{Cl}{C}C\equiv CH \underset{slow}{\rightleftharpoons} (CH_2)_2\overset{Cl}{C}C\equiv C^{\ominus} \longrightarrow \\ (CH_3)_2C=C=CHCl \underset{slow}{\rightleftharpoons} (CH_2)_2C=C=\overset{\ominus}{C}Cl \rightarrow \end{array} \left[\begin{array}{c} (CH_3)_2\overset{\oplus}{C}\text{-}C\equiv C^{\ominus} \\ \updownarrow \\ (CH_3)_2C=C=C: \end{array}\right] \xrightarrow[solvent]{} (CH_3)_2\overset{OEt}{C}C\equiv CH$$

Buraway and Spinner (40) observed that for 3-chloro-3-methyl-1-alkyl-1-butyne there is no second-order reaction in a basic solution. This supports Hennion and coworkers' suggestion that the acetylenic hydrogen is lost.

Hennion and coworkers (41), (42), (43), (44) theorized that because of the positive charge on the number three carbon, the intermediate would react with bases to form solvolytic products. They found the reaction of 3-chloropropynes with amines to be a general method for the preparation of higher amines, and with alcohols to be a general method for the preparation of ethers. Zaugg, Sweet and Stone (45) observed the following reaction of propargylbromide with a secondary amine:



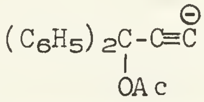
They took this as an indication of the following intermediate.



$$\left[\overset{\oplus}{C}H_2\text{-}C\equiv C^{\ominus} \leftrightarrow CH_2=C=C: \leftrightarrow \overset{\ominus}{C}H_2\text{-}\overset{\oplus}{C}\equiv C\right]$$

Hartzler (46), (47) obtained evidence that the intermediate in the alcoholysis of tert-acetylenic chlorides is a carbene. He formed cyclopropane rings by the reaction of 3-chloro-3-methylbutyne with potassium t-butoxide in the presence of styrene and in the presence of cyclohexene. Hartzler also studied the stereochemistry of the addition of dimethylvinylidenecarbenes (48) to cis and trans-2-butene. Stereospecific addition was observed. The fact that dimethylvinylidenecarbene adds stereospecifically to olefins suggests that the carbene is in the singlet state.

Cadiot (49) reports the reaction of 3,3-diphenylpropyne-3-ol, in the presence of base and acetic anhydride, to form tetraphenylhexapentaene. Hartzler (50) suggested that this reaction proceeds by way of the reaction of diphenylvinylidenecarbene with anion XIII.



$$(C_6H_5)_2\underset{\displaystyle OAc}{\underset{|}{C}}-C\equiv\overset{\ominus}{C}$$

XIII

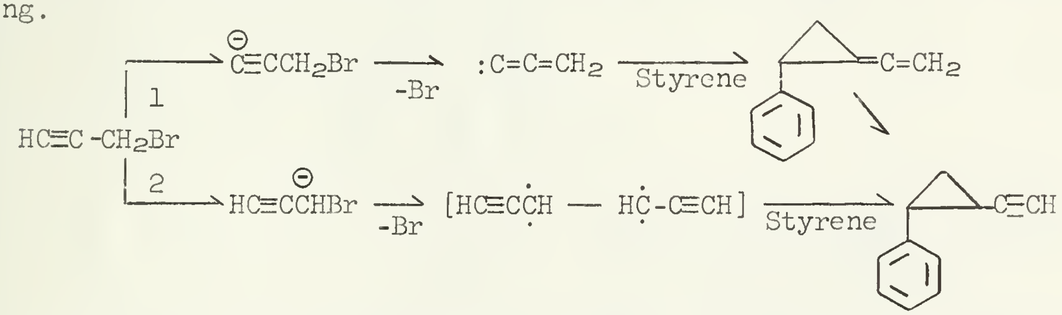
Shiner and Wilson (51) found that deuterium exchanges of the active hydrogen of 3-chloro and 3-bromo-3-methylbutyne is appreciably faster than the base promoted solvolysis. This is in agreement with what Hine (7a) found for the hydrolysis of chloroform, but does not agree with Hennion's (39) mechanism for the hydrolysis of 3-chloro-3-methylbutyne in which he proposed that the loss of the active hydrogen is the slow step. Shiner and Wilson also found the basic hydrolysis of 3-chloro- and 3-bromo-3-methylbutyne to have a salt effect remarkably similar to that observed by Hine for the basic hydrolysis of chloroform (7a), (7b).

Hartzler (52) has also made dimethylvinylidene carbene by the alcoholysis of 1-chloro-3-methyl-1,2-butadiene. He found that the reactivities of the dimethylvinylidenecarbene , as found by reaction with olefins, to be independent of whether they were derived from the diene or the acetylene. This indicates that the carbene is independent of its source.

While discussing the reaction of vinylidenecarbenes with bases, we considered a reaction of propargyl bromide with an amine. Zaugg, Sweet and Stone (45) proposed the following intermediate for the reaction:

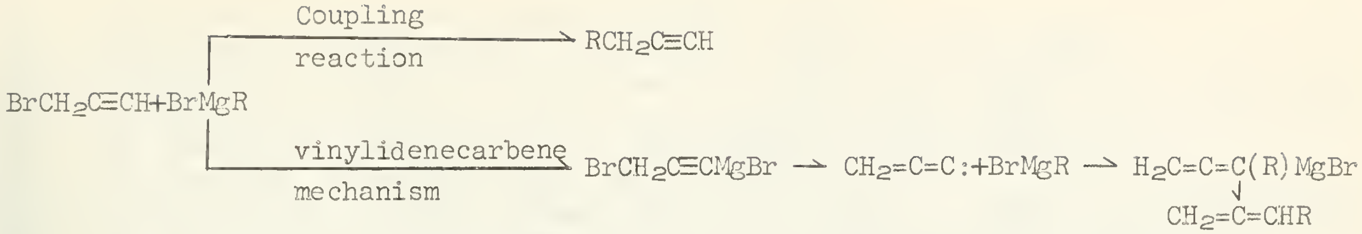
$$\left[\overset{\oplus}{C}H_2-C\equiv\overset{\ominus}{C} \leftrightarrow CH_2=C=C: \leftrightarrow \overset{\ominus}{C}H_2-C\equiv\overset{\oplus}{C}\right]$$

Hartzler (50) has obtained additional proof of a carbene intermediate in the reaction of propargyl bromide with base. He found that addition of propargyl bromide to a slurry of potassium tert-butoxide in styrene led to the formation of a cyclopropane ring.



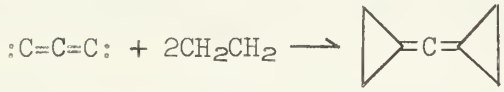
At least part of the reaction goes by mechanism 1 but the study of the mechanism is complicated by the fact that the allene is labile and rearranges to the acetylene.

Serratosa (53a) suggested that certain previously reported reactions of propargyl bromide with Grignard reagents (53b), (53c) go through vinylidenecarbenes. He suggested a vinylidenecarbene intermediate for the reaction of alkylmagnesium bromides with propargyl bromide at temperatures below zero degrees. At 40° the vinylidenecarbene mechanism competes with the coupling reaction. For arylmagnesium bromide the vinylidenecarbene mechanism competes with the coupling reaction at temperatures below zero degrees.



Skell and Klebe (54) have studied the stereochemistry of propargylene (C_3H_2), formed by the photolysis of diazopropyne. Propargylene does not add stereospecifically to olefins.

Skell and Wescott (55) have synthesized a dicarbene (C_3), and have observed the following reaction:



Bayes (56), (57) has reported that the photolysis of carbon suboxide in the presence of ethene gives as products carbon monoxide and allene. Bayes suggested the following as an intermediate: :C=C=O. Palmer and Hirt (58) suggested that nuclear carbon may be the intermediate that reacts with ethene. MacKay, Polak, Rosenberg, and Wolfgang (59) studied the reaction of recoil carbon-11 using ethene as a carrier-gas. The two main products containing carbon-11 were acetylene, in above a 30% yield, and allene, in a 18% yield. These results were essentially unaffected by the presence of oxygen or neon in the carrier-gas. The main product of the reaction of carbon suboxide with ethene is allene. This result indicates carbon is not the reactive intermediate involved. Bayes (60) has suggested that there are two forms of C_2O, one a singlet and one a triplet. Using monochromatic light, he found at short wave lengths (below 2600 A°) the reaction of the intermediate is unaffected by O_2, indicating a singlet, while at longer wave lengths the reaction is greatly affected, indicating a triplet (61).

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DIAZENE INTERMEDIATES

Reported by James A. Bonham October 12, 1964

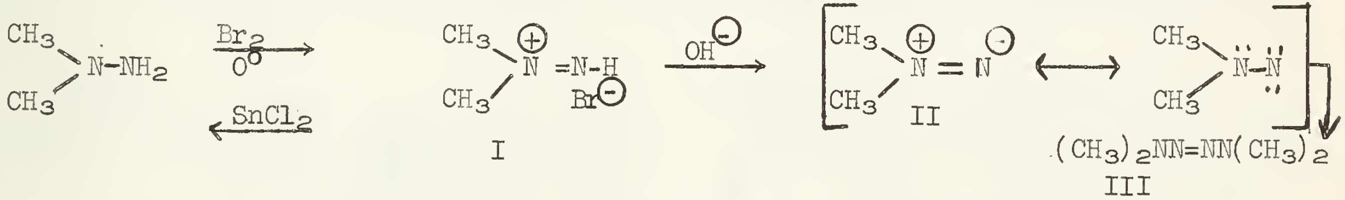
INTRODUCTION

Compounds of the type II, have been proposed as intermediates in various reactions of 1,1-disubstituted hydrazines and their derivatives. Particularly, the oxidation of 1,1-disubstituted hydrazines, the base decomposition of 1,1-disubstituted-2-sulfonylhydrazines and the thermal decomposition of their salts, the sodium hydrosulfite reduction of nitrosamines, and the deamination of secondary amines with difluoroamine have appeared in the literature. An unfortunate situation exists concerning the nomenclature of this intermediate. It has been termed an azamine[1], aminonitrene, aminoimidogen[2], and diazene. The latter will be used in this abstract. The majority of evidence is based upon the nature of the products obtained, and in the similarities of products resulting from different reactions.

I. Oxidation of 1,1-Disubstituted Hydrazines and Sodium Hydrosulfite Reduction of 1,1-Disubstituted Nitrosamines. -- The two electron oxidation of 1,1-disubstituted hydrazines using a variety of oxidizing agents usually proceeded to form the so-called normal oxidation product, a tetrazene[3]. McBride and coworkers[4] studied quantitatively

$$R_2NNH_2 \xrightarrow{[O]} \underset{\text{a tetrazene}}{R_2NN = NNR_2}$$

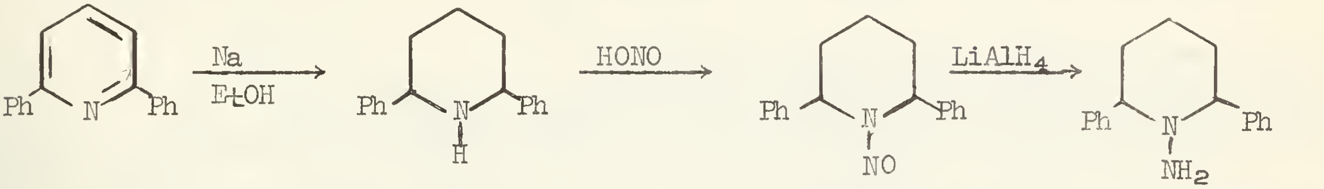
the two electron oxidation of 1,1-dimethylhydrazine with bromine in acidic solution, and were the first to present definite evidence for the existence of a diazene as its conjugate acid. No tetramethyltetrazene (III) was detected in the ultraviolet spectrum of the resulting acidic reaction mixture. However, careful neutralization resulted in the formation of the expected tetrazene as indicated by the absorption spectrum. Reacidification of the alkaline solution gave no reversible change. Treatment of the initially oxidized acidic solutions with stannous chloride gave 1,1-dimethylhydrazine back in 88 % yield based on the gravimetric separation as the oxalate salt. Stannous chloride did not reduce tetramethyltetrazene under the same conditions. A new class of diazo-like compounds was postulated, (II), which exhibited remarkable stability as their conjugate acids (I). Neutralization of the diazenium ion (I) to the diazene, followed by a coupling reaction between the two species accounted for the formation of the tetrazene (III). To further substantiate the existence of I, 1,1-dimethyldiazenium perchlorate, $(CH_3)_2\overset{\oplus}{N}{=}NH\overset{\ominus}{ClO_4}$, was prepared by the reaction of iodine, silver perchlorate, and 1,1-dimethylhydrazine in anhydrous ether, but was not completely characterized. The combination of separately oxidized solutions of different 1,1-dialkylhydrazines and then neutralization resulted in the statistical formation of the mixed tetrazene derivatives[5].



It seems possible that the acidic bromination product (I) could also be the covalent species, $(CH_3)_2NNHBr$, or its protonated form. The diazenium ion (I) in a variety of acidic solvents was reported to have an ultraviolet absorption maximum at 280 mμ. (ϵ 150), which was dependent upon the solvent anion[5]. However, the spectrum was taken using the crude oxidation mixture, with no assurance that the observations weren't due to a minor impurity. Evidence from the preparation of 1,1-dimethyldiazenium perchlorate may be questionable due to the poor characterization. The reactions of the diazenium ion (I) described in section III may also be explained using the covalent species as its protonated form. Nevertheless, this diazenium species will be written in the ionic form (I) in this abstract.

The first anomalous oxidation was reported in 1900 by Busch and Weiss[6] in the oxidation of 1,1-dibenzylhydrazine with yellow mercuric oxide. The products were bibenzyl and nitrogen. Kenner and Knight[7] later postulated that a diazene was involved in this reaction.

Evidence regarding the stereochemistry associated with the oxidation of cyclic 1,1-disubstituted hydrazines[8-12] was provided using cis- and trans-1-amino-2,6-diphenylpiperidines (VI), which were prepared as shown[12]. The trans-2,6-diphenylpiperidine (IV-trans) was resolved using dibenzoyl-d-tartaric acid monohydrate. No attempt



IV-cis (39%)
IV-trans (50%)

V-cis (89%)
V-trans (64%)

VI-cis (88%)
VI-trans (50%)

was made to resolve the hydrazine (VI). However, the trans-isomer (VI-trans) was converted to the cis-compound (VI-cis) using lithium aluminum hydride in refluxing ether. Under similar treatment the cis-compound was recovered unchanged. The oxidation of the stereoisomers using mercuric oxide in ethanol gave products with retention of configuration at the α-carbon atoms as indicated in figure 1. Some cis-product (VII-cis) was isolated from the trans-reactant (VI-trans) in low yield. No control experiment, however, was performed to determine whether VI-trans was converted to the cis-reactant under the oxidation conditions. Olefin formation (VIII) was shown to probably occur through an E_2-type mechanism[19,20].

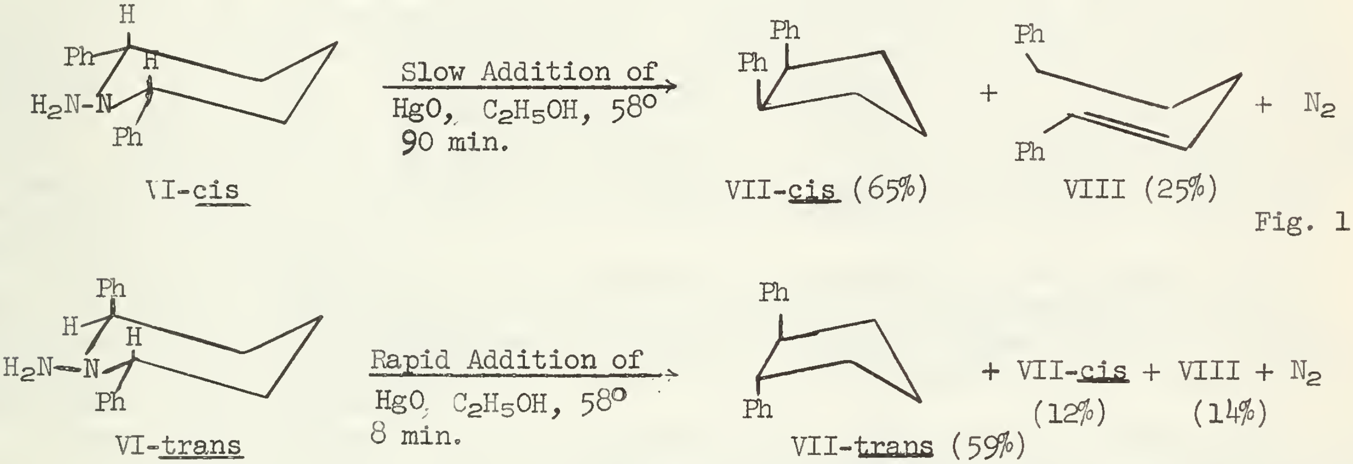
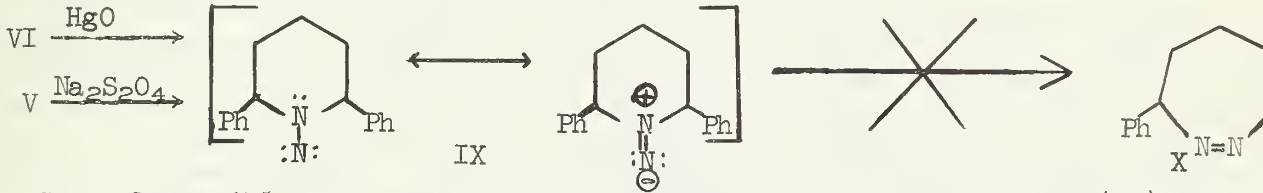
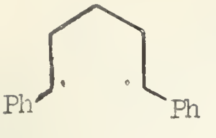


Fig. 1

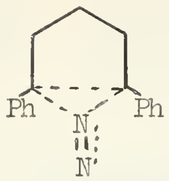
The products and product ratios obtained from the sodium hydrosulfite reduction[13] in basic media of the cis- and trans- nitrosamines (V) were the same as those obtained in the hydrazine oxidations. Similar reductions of N-nitrosodibenzylamines[14] and N-nitrosoazetidine[15] also occurred with nitrogen evolution and formation of coupled products. It has been postulated that these reactions proceeded in a manner similar to the oxidation of the hydrazines via a diazene intermediate (IX).



Several possible major pathways are possible by which the diazene (IX) could break down. Rearrangement to the isomeric seven-membered azo compound (X) is one possibility. However, it was shown[16] that the azo compound (X) gave a mixture of cis- and trans-1,2-diphenylcyclopentanes when decomposed, but the reaction half-life was ca. five hours at 61°. Also, X isomerized to the cyclic hydrazone in a reaction competing with the decomposition. A biradical (XI) is also possible, except the observed stereoretention must be rationalized by assuming that bond formation occurred more quickly than rotation of the radical centers. Certainly, many electronic factors are present which influence the products formed, but a main contribution to the stereospecificity would be



XI



XII - cis or trans

eclipsing of the phenyl rings in the transition state. Any free fragments formed which could rotate might favor the trans-1,2-diphenylcyclopentane. A concerted loss of nitrogen as formally represented in XII would be the favored explanation of these results.

To avoid the possibility that the observed stereoretention was a result of a geometric restriction associated with a cyclic structure, optically active N-amino-α,α'-dimethyldibenzylamine (XVI) and the corresponding N-nitroso compound (XV)

$$RN{=}C(CH_3)Ph \xrightarrow[Pd/C]{H_2} R_2NH \xrightarrow{HONO} R_2NNO \xrightarrow[EtOH]{Na} R_2NNH_2$$

XIII, $R{=}Ph(CH_3)\overset{*}{C}H$ XIV XV XVI

were prepared as shown[17]. The formation of XIV was shown to proceed with a high degree of asymmetric induction to generate a new optically active center. Conversion of XIV to give the D-(-)-α methylbenzylamine (44 %) supported the D,D-configuration of the substituted dibenzylamine (XIV). Further preparative steps did not involve participation of the asymmetric centers, and the resulting nitroso compound (XV) and hydrazine (XVI) were reconverted to XIV in high yield and optical purity. Both the nitroso compound (XV) and hydrazine (XVI) were optically stable under treatment with base, thus assuring the final observations were due to the oxidation and reduction.

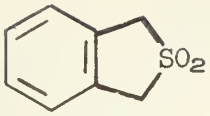
Reduction of the nitroso compound (XV) with sodium hydrosulfite in base gave nitrogen (90%), crystalline meso-2,3-diphenylbutane (21%), and a mixture of liquid isomers of 2,3-diphenylbutane (42%, $[\alpha]_D^{20}$-45°). Similarly, mercuric oxide oxidation of the hydrazine (XVI) produced nitrogen (99%), meso-2,3-diphenylbutane (31%), and the liquid isomers (45%, $[\alpha]_D^{20}$-36°). The specific rotation of optically pure 2,3-diphenylbutane is 95-99°. The formation of the meso-hydrocarbon plus racemization tended to indicate that a completely concerted process was not operative. It was noted, however, since there was partial retention the fragments are probably relatively short lived in comparison with time for racemization.

The intramolecular nature of the formation of bibenzyls has been demonstrated by the reduction of unsymmetrically substituted N-nitroso-1,1-dibenzylamines[14] and the oxidation of 1,1-dibenzylhydrazines[18]. Yields of bibenzyls ranged from 12 to 79% and no intermolecular crossover products were detected. Less than one-half percent styrene was formed in the reduction.

Comparison of the results of the non-cyclic derivatives with the cyclic cases led to no definite conclusion. If the reactions involved fragmentation of a diazene intermediate and subsequent combination, then the crossover experiments indicated the fragments are effectively trapped within a solvent cage. The partial racemization observed suggested some fragmentation. Another alternative which was suggested involved racemization of the diazene intermediate via its anion (removal of proton on carbon). Such species have been postulated (see section IV). Therefore, these reactions did not distinguish between a concerted, ionic, or radical pathway.

Urry[21] has recently detected the minor products in the oxidative reactions of 1,1-dialkylhydrazines and their derivatives which do not lose nitrogen. Normally, these reactions were believed to yield only tetraalkyltetrazenes. For example, 1,1-dipropylhydrazine gave in addition to tetrapropyltetrazene, the propylhydrazone and dipropylhydrazone of propionaldehyde as major products, and propanol, azopropane, propane, and nitrogen as minor products. High concentrations of aqueous base, higher temperature, and low concentrations of the intermediate diazenes lead to more rearrangement.

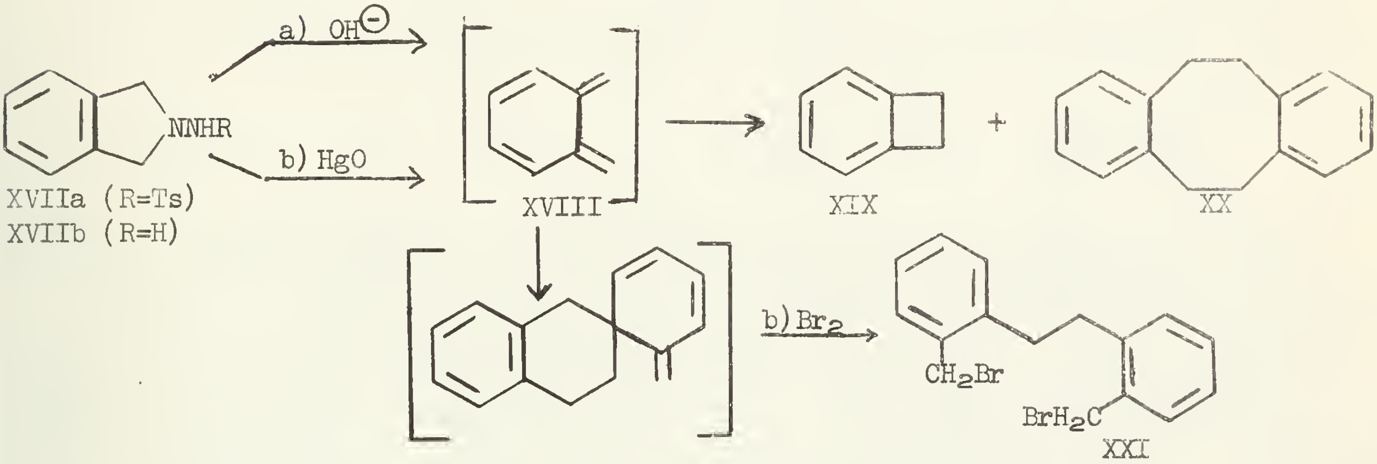
II. Oxidative Reactions of 1-Aminodihydroisoindoles.--The oxidation of 1-aminodihydroisoindoles as well as the base degradation of their benzenesulfonyl derivatives are unique in comparison to the saturated cyclic cases. Conjugation is possible between the incipient fragments from the C-N bond cleavages. Baker and coworkers[22,23] isolated benzocyclobutene (14%, XIX), 1,2,5,6-dibenzocyclooctadiene (12%, XX), and o-xylene (2%) from the alkaline decomposition of XVIIa. The products were identified by spectral criteria and vapor phase chromatography. The authors suggested the reaction proceeded via an o-quinodimethane intermediate (XVIII). Their analogy was the pyrolysis



XXII

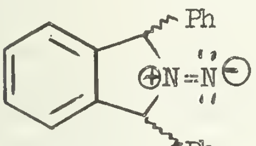
of XXII in the molten state, which gave the same products[24]. The o-quinodimethane (XVIII) has been efficiently trapped from the pyrolysis of XXII or its derivatives using a dieneophile[25,26], but has not been attempted in the case of the dihydroisoindoles (XVII).

Fig. 2



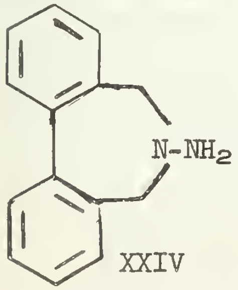
How far product comparisons may be extended is certainly questionable, especially due to the effect of varying reaction conditions. For example, XXII in boiling diethylphthalate gave only the benzocycloöctadiene ([26],XX). Using the technique of Errede[27], addition of bromine to the crude reaction mixture from the mercuric oxide oxidation of XVIIb resulted in the isolation of the dibromide of the o-quinodimethane dimer ([28], XXI).

Similar investigations[23,28] were performed to provide a method for the preparation of 1,2-diphenylbenzocyclobutenes. Carpino[28] found that the oxidation of trans-1,3-diphenyl-2-aminodihydroisoindole with meruric oxide in methylene chloride gave trans-1,2-diphenylbenzocyclobutene (62%). Similar treatment of the cis-1,3-diphenyl-2-aminodihydroisoindole produced a low yield of both cis- and trans-1,2-diphenylbenzocyclobutene. However, oxidation of the cis-isoindole derivative with activated manganese dioxide gave the cis-1,2-diphenyl product in 27% yield. No explanation was proposed for this difference. The pyrolysis of the 1,3-diphenyl derivative of XXII at 250^0 in diethylphthalate gave primarily 9-phenyl-9,10-dihydroanthracene, which was also formed from the thermal rearrangement of 1,2-diphenylcyclobutene[26]. Carpino suggested that no definite prediction of sterochemistry could be made in the case of a reaction proceeding through an o-quinodimethane intermediate, and he favored a concerted expulsion of nitrogen and ring contraction from XXIII to explain the observations. This is certainly possible. However, an o-quinodimethane intermediate may not be ruled out on this basis. A stereospecific formation of o-quinodimethane intermediates from the cis- and trans-1,2-diphenyldiazenes (XXIII) and followed by a stereospecific ring closure is a plausible alternative. Criegee[29], for example, has observed stereospecific ring openings in the thermal rearrangement of cis- and trans-1,2,3,4-tetramethylcyclobutene.

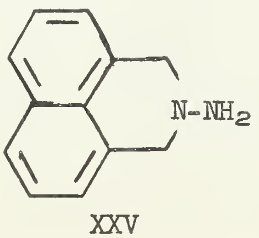


XXIII

Mercuric oxide oxidation of 6-amino-5,7-dihydrodibenzo[ce]azepine (XXIV) as well as the base degradation of its benzenesulfonylhydrazine derivative gave the expected 9,10-dihydrophenanthrene[30]. However, 2-amino-2,3-dihydro-1H-benz[de]isoquinoline (XXV) did not lose nitrogen, either by oxidation or alkaline treatment of the sulfonylhydrazine derivative. The only product isolated other than starting material was the corresponding tetrazene (15%). To be certain of the structures, (XXIV) and (XXV), the isomeric cyclic hydrazines and azo compounds were prepared. The difference in the reactivity of XVII and XXIV on the one hand and XXV on the other could be rationalized by the necessity of an o-quinodimethane type intermediate.



XXIV



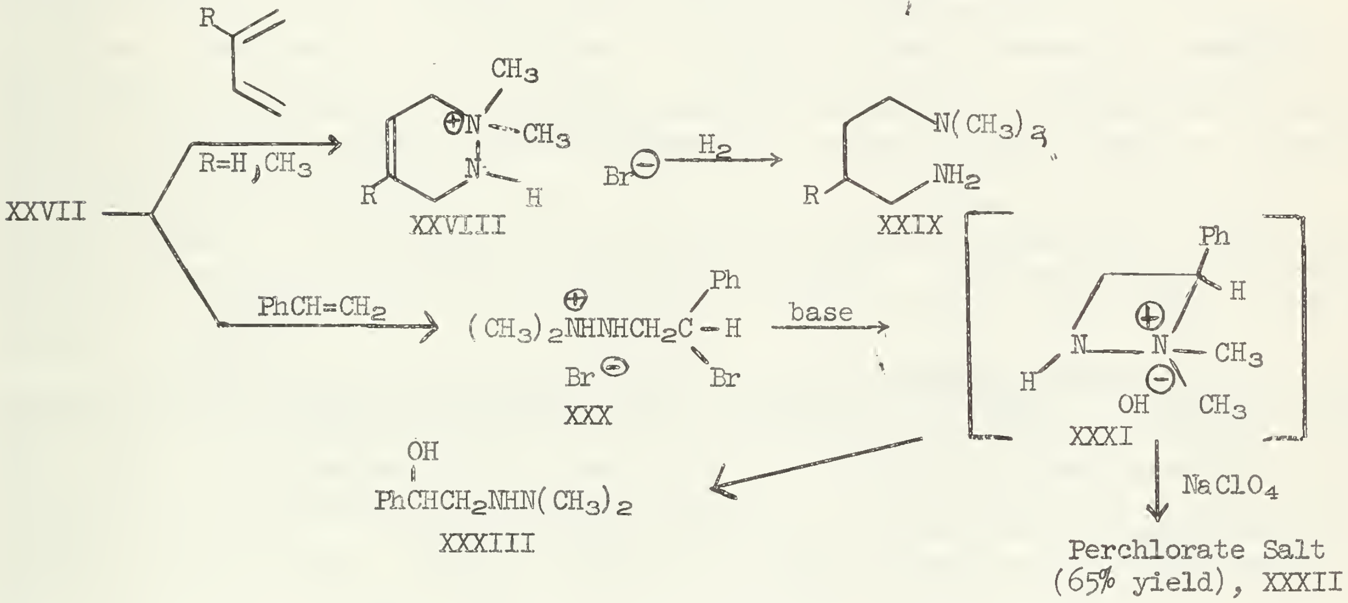
XXV

III. Diazenium Ions, $R_2\overset{\oplus}{N}=NH$.--McBride and coworkers provided evidence for the existence of diazenium ions, the conjugate acids of diazenes (see section I). Further investigations have illustrated their electrophilic character and their production. Urry[31,32] discovered that 1,1-dimethyldiazenium bromide (XXVII) underwent electrophilic addition to 1,3-dienes and styrenes. With successive additions of bromine to 1,1-dimethylhydrazinium bromide (XXVI, methyl singlet δ 3.39 p.p.m.), the appearance in the nuclear magnetic resonance spectrum in D_2O at 0° of the methyl peak (singlet δ 4.78 p.p.m.) of 1,1-dimethyldiazenium bromide (XXVII) was easily observed. The chemical shifts of the methyl protons of XXVI and XXVII were concentration independent.

$$\underset{\text{XXVI. }Br^{\ominus}}{(CH_3)_2\overset{\oplus}{N}H\text{-}NH_2} + Br_2 \xrightarrow{HBr} \left[\underset{\text{XXVII}}{(CH_3)_2\overset{\oplus}{N}=NH} \longleftrightarrow \underset{Br^{\ominus}}{(CH_3)_2\ddot{N}\text{-}\underset{\oplus}{\ddot{N}H}}\right]$$

Whenever the acidic solutions of XXVII were made basic, tetramethyltetrazene (n.m.r. in D_2O-HBr, methyl singlet δ 2.86 p.p.m.) was isolated in near quantitative yield.

Treatment of solutions of XXVII with 1,3-butadiene[31] or isoprene[32] resulted in the formation of 1,1-dimethyl-Δ^4-tetrahydropyridazinium bromide (73%, XXVIII, R=H) and 1,1,4-trimethyl-Δ^4-tetrahydropyridazinium bromide (76%, XXVIII, R=CH_3). Styrene[32] reacted with XXVII in a hydrobromic acid solution at 0° and gave 1,1-dimethyl-2-(2-bromophenylethyl)-hydrazinium bromide (76%, XXX). The nuclear magnetic resonance spectrum consisted of an N-methyl singlet δ 3.15 p.p.m., methylene doublet δ 3.91 p.p.m., benzylic hydrogen triplet δ 5.60 p.p.m., and phenyl multiplet δ 7.45 p.p.m. Further characterization by hydrogenation to 2-phenylethylamine (76%), 1,1-dimethyl-2-(2-phenylethyl)hydrazine (15%), and dimethylamine confirmed the structure.



Reaction of XXX with dilute sodium carbonate followed by the addition of a saturated solution of sodium perchlorate resulted in the formation of the previously unknown 1,1-dimethyl-4-phenyl-1,2-diazetidinium perchlorate (XXXII). The nuclear magnetic resonance spectrum in D_2O consisted of two methyl peaks at δ 2.91 and δ 3.62 p.p.m., methylene triplets at δ 4.26 and δ 4.71 p.p.m., benzylic triplet at δ 6.25 p.p.m., and phenyl singlet at δ 7.74 p.p.m. Microanalysis confirmed the stoichometry and hydrogenation gave the known 2-dimethyl-amino-2-phenylethylamine (36%).

Compound XXX dissolved in a sodium hydroxide solution and the nuclear magnetic resonance spectrum indicated that XXXI was first formed. As the spectrum of XXXI disappeared ($t_{1/2}$ in 4N NaOH 15 min., 1.16N 2.5 hrs.), the spectrum of 1,1-dimethyl-2-(2'-hydroxy-2'-phenylethyl)hydrazine (XXXIII) appeared, which was isolated in a subsequent experiment in 43% yield. With dilute acid XXXIII fragmented to yield dimethylamine, ammonia, formaldehyde, benzaldehyde, 1,1-dimethylhydrazine, and phenylacetaldeyde. Similar experiments were performed with varying success on 2-phenyl propene and indene.

Lemal[33] has presented evidence for the production of 1,1-dialkyldiazenium ions in the anion exchange of 1,1-dimethyl-2-methane sulfonylhydrazine (XXXIV) with sodium toluenesulfinate (XXXV). When excess XXXV was present in an aqueous solution, compound

XXXVI crystallized in nearly quantitative yield. In methanol, however, a homogeneous equilibrium was established. The exchange was followed by nuclear magnetic resonance

$$\underset{\text{XXXIV}}{(CH_3)_2NNHSO_2CH_3} + \underset{\text{XXXV}}{\overset{\oplus\ \ominus}{NaTs}} \rightleftharpoons \underset{\text{XXXVI}}{(CH_3)_2NNHTs} + \underset{\text{XXXVII}}{\overset{\oplus\ \ominus}{NaO_2SCH_3}}$$

spectroscopy using the differences in the chemical shifts of the methyl protons in XXXIV and XXXVII. The following facts were observed: a) exchange was accelerated by increasing solvent polarity; b) initial rates were not enhanced by increasing the concentration of the sulfinate anion (XXXV); c) succesive replacement of the methyl groups on nitrogen with phenyl substituents hindered exchange, i.e., $(CH_3)_2NNHSO_2CH_3 > CH_3(Ph)NNH-SO_2CH_3 > Ph_2NNHSO_2CH_3$; and d) electron withdrawing groups on sulfur accelerated initial rates. These observations were consistent with the hypothesis that ionization of the sulfonylhydrazine (XXXIV) to 1,1-dimethyldiazenium ion and sulfinate ion was rate determining, followed then by rapid anion exchange.

$(CH_3)_2N\overset{\ominus}{N}SO_2CH_3$
XXXVIII

This simple ionization was shown to require a lower free energy of activation than loss of sulfinate ion from the conjugate base (XXXVIII) of the sulfonylhydrazine. Solutions of XXXIV in strong base were very stable, and when combined with sodium benzenesulfinate, exchange did not occur. However, when ca. 0.5 - 1 equivalent of base was present, rapid decomposition occurred in the cold. The explanation presented was that the weakly acidic sulfonylhydrazine, which was in equilibrium with its conjugate base, was present in sufficient concentration and ionized to the 1,1-dimethyldiazenium ion. Rapid attack of base upon this cation to give a diazene (removal of N-proton) or to give a 1,3-dipolar species (removal of carbon proton) ([34],LIV) accounted for product formation (see section IV).

This phenomenon is very interesting. Normally, α-eliminations, e.g., formation of carbenes or the alkaline decomposition of tosylhydrazones[35], proceed via expulsion of an anion from a conjugate base or through a concerted mechanism. Lemal has pointed out that not all sulfonylhydrazines are as stable as XXXIV in base, but the fact that decomposition of a given 1,1-dialkyl-2-sulfonylhydrazine is faster in dilute than in concentrated base appears to be general.

Wawzonek[36] has postulated that 1,1-dimethyl- and 1,1-dibenzyl-2-toluenesulfonylhydrazine underwent a dissociation into diazenium ions and sulfinate ions. These species were then responsible for the acid hydrolysis products. This was based upon the similarities of products from the acid hydrolysis of the diazenium bromide salt prepared according to McBride.

IV. Alkaline Degradation of 1,1-Disubstituted-2-sulfonylhydrazines and the Thermal Decomposition of Their Sodium Salts.--These reactions may formally be viewed as arising from the α-elimination of sulfinic acid or sulfinate anion providing a diazene intermediate, which may decompose by one or several of the competing pathways available depending upon the substituents and reaction conditions. In the case of the 1,1-dibenzyl-2-sulfonylhydrazines[37], they react analogously to the mercuric oxide oxidations to yield nitrogen and bibenzyls. The formation of bibenzyls was shown to be intramolecular also[18].

Carter and Stevens[38] concluded from the kinetics of the decomposition of several 1-aryl-1-benzyl-2-toluenesulfonylhydrazines (XXXIX) that the reactions showed first order kinetics with respect to the anion of the sulfonylhydrazine (XL). The products

$Bz(Ar)N\overset{\ominus}{N}Ts$
XL

were the arylhydrazones of benzaldehyde. The kinetics were determined by following the rate of disappearance of base, and it was found that the velocity was unaffected by alkali in excess of one equivalent. No attempts were made to vary the concentration of the sulfonylhydrazine (XXXIX), or to use a base concentration of less than one equivalent. They concluded that the loss of sulfinate anion from the conjugate base (XL) was rate determining. This may well be the existing situation, which is analogous to the base decomposition of tosylhydrazones, but the amount of data reported was not sufficient to make it unequivocal. Conceivably, a mechanism involving ionization of the sulfonylhydrazine (XXXIX) to a diazenium ion and sulfinate ion (see section III) can be made consistent with the data using certain assumptions.

The thermal decomposition of 1,1-dialkyl-2-benzenesulfonylhydrazine sodium salts has provided further evidence regarding the chemistry of diazenes. Lemal and coworkers[39,40] have recently investigated the reactions illustrated in fig. 3. The decomposition[39] of

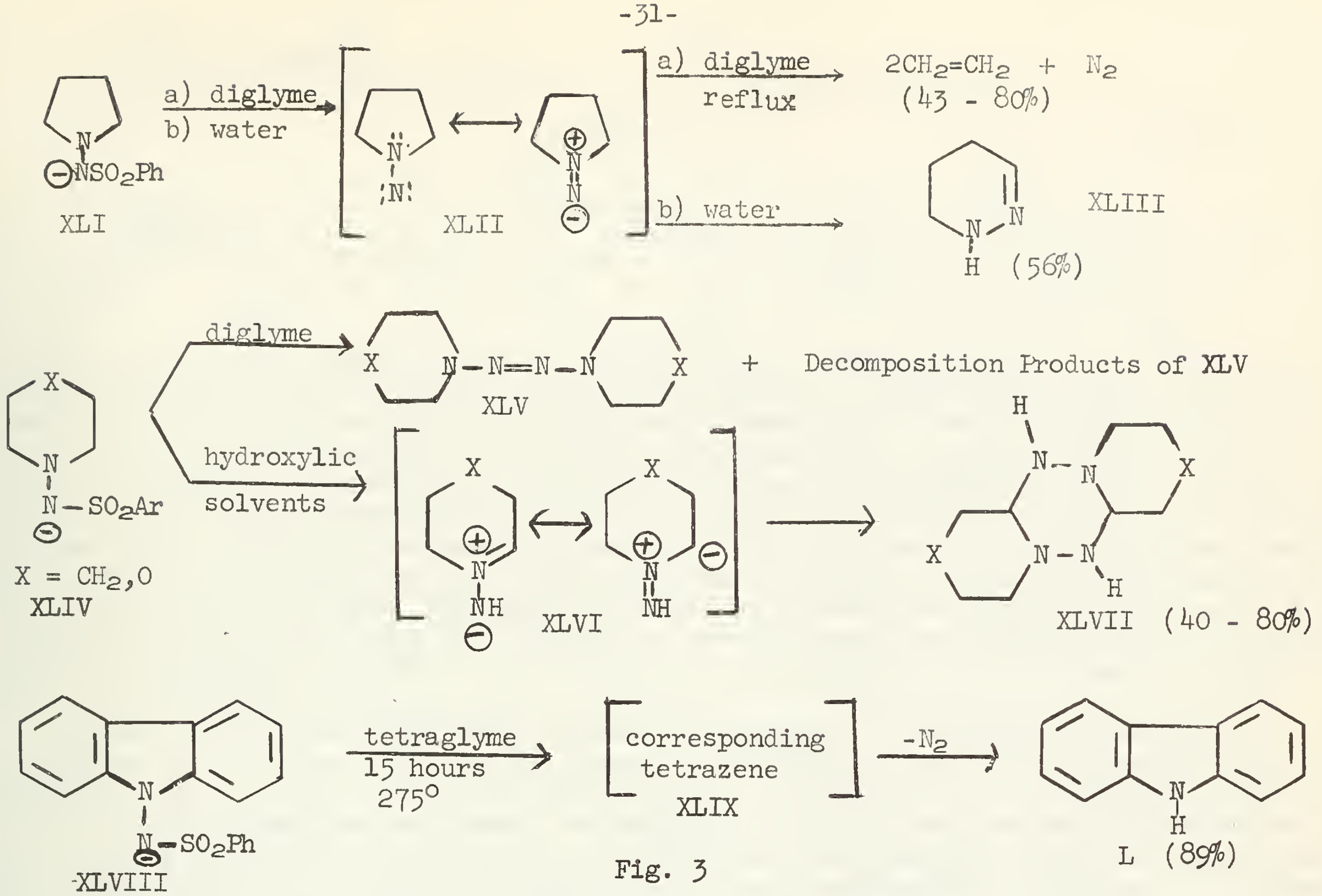

a) diglyme
b) water
XLI
XLII
a) diglyme reflux
$2CH_2=CH_2 + N_2$
(43 - 80%)
b) water
XLIII
(56%)
diglyme
XLV
+ Decomposition Products of XLV
hydroxylic solvents
X = CH_2,O
XLIV
XLVI
XLVII (40 - 80%)
tetraglyme
15 hours
275°
corresponding tetrazene
XLIX
$-N_2$
XLVIII
L (89%)

Fig. 3

N-benzenesulfonamidopyrrolidine sodium salt (XLI) in diglyme gave unreproducible yields due to an experimental technique. Only nitrogen and ethylene were formed, no cyclobutane being detected. The authors suggested that the diazene does not collapse to nitrogen and a 1,4-diradical intermediate. This was supported by the decomposition of N-benzenesulfonamidopiperidine ([40],XLIV, X=CH_2) in diglyme, which gave the corresponding tetrazene (XLV) and no nitrogen evolution.

The unsaturated analog of XLI, i.e., N-tosylamidopyrrole, was recovered unchanged when heated at 225° for 1 hour in tetraglyme, but gave pyrrole (10%) plus tars upon heating at 275° for 8 hours. In the case of N-benzenesulfonamidocarbazole (XLVII), decomposition occurred to give a high yield of carbazole, presumably through the tetrazene (XLIX) as illustrated. Tetrazene formation was rationalized via attack of the intermediate diazene upon XLVIII, followed by loss of nitrogen to a carbazole radical and hydrogen abstraction from the solvent to give L. To test this hypòthesis, the tetrazene (XLIX) was prepared and subjected to the reaction conditions for five minutes. The yield of carbazole (L) was almost quantitative (94%). Appropriate control experiments were performed to exclude direct N-N bond cleavage in XLVIII.

The solvent dependency in the course of the thermal decompositions of a number of 1,1-dialkyl-2-benzenesulfonylhydrazine sodium salts to hydrazones has been investigated [34,40]. Tetrazenes were the major products in aprotic solvents, such as diglyme or tetraglyme, and the hydrazones were favored in protic media, diethylene glycol (DEG) or water, with or to the exclusion of tetrazenes (e.g., see fig. 3 and 4). The formation of hydrazones has been termed the "Diazene-Hydrazone" rearrangement[34].

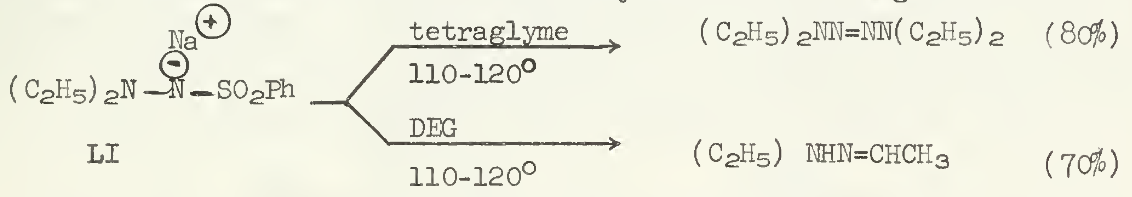

$(C_2H_5)_2N-\overset{\ominus}{N}-SO_2Ph$ $Na^{\oplus}$
LI
tetraglyme
110-120°
$(C_2H_5)_2NN=NN(C_2H_5)_2$ (80%)
DEG
110-120°
(C_2H_5) $NHN=CHCH_3$ (70%)

Fig. 4

The most obvious pathway (a) for rearrangement to the hydrazones was a simple 1,2-alkyl shift to give the azo compound from LI (see fig. 5). Azo compounds are known to undergo tautomerizations to hydrazones easily. However, the appropriate control experiment in which azoethane (LII) was stable to the reaction conditions proved that this mechanism was not the favored pathway. Conceivably, diaziridine (LVI) could also be an

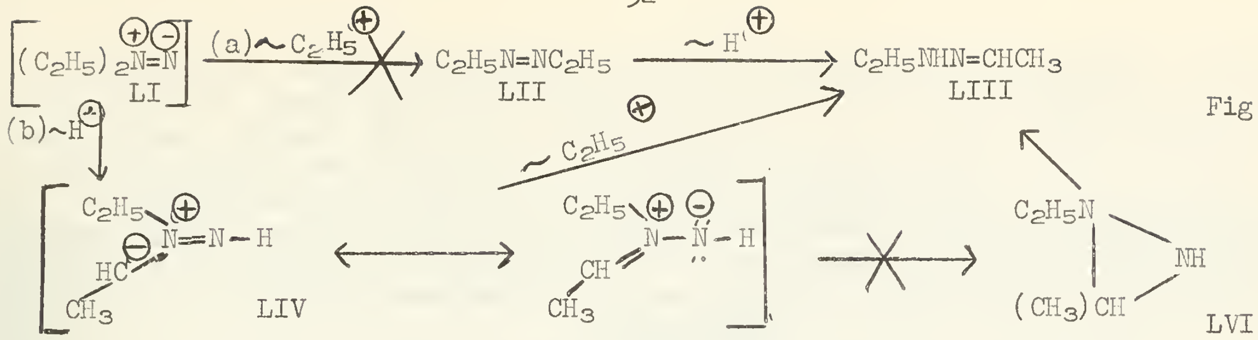


Fig. 5

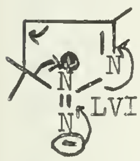
intermediate in the proposed scheme, but it was also stable to the reaction conditions proved that this mechanism was not the favored pathway. Conceivably, diaziridine (LVI) could also be an intermediate in the proposed scheme, but it was also stable to the reaction conditions. The remaining pathway (b) was consistent with these experimental details to explain the formation of the ethylhydrazone of acetaldehyde (LIII). It could also be extended to rationalize the formation of products such as XLIII and XLVII (See fig. 3) In the aprotic solvent no pathway was available to facilitate a concerted proton transfer from carbon to nitrogen, and no proton source to permit stepwise tautomerism proceeding via a diazenium ion. In the protic media the diazene was postulated to be in equilibrium with its conjugate acid, either or both of which was possibility the precursor of the zwitterion of the type (LIV). This solvent facilitated proton transfers not possible in the aprotic media.

However, Urry[41] has found that the same enhancement of rearrangement occurred in triethylamine, a solvent that has no hydroxyl functions to facilitate formation of a zwitterion of the type (LIV). This would indicate that LIV is not a necessary intermediate in the hydrazone rearrangement. He suggested that the base removes a proton from the carbon atom adjacent to nitrogen in the diazene, and that the resulting anion undergoes rearrangement. This was also supported in that rearrangement is favored by increased base concentration and strength.

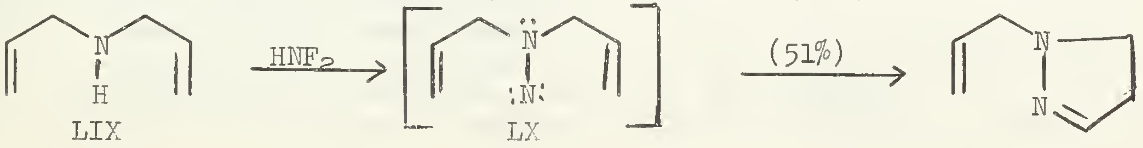
Lemal[42] has performed an N^{15} labeling experiment that demonstrated that 1-benzyl-1-phenyl-2-benzenesulfonylhydrazine goes by a different mechanism than postulated in fig. 5, which would require migration of the phenyl group. He noted, however, that a duality of mechanisms was possible due to the large difference in substituents involved.

V. Formation of Diazenes from Secondary Amines.--Recently, Bumgardner and coworkers[15] observed that difluoroamine, HNF$_2$, functioned as an efficient and direct deaminating reagent for aliphatic and aromatic primary amines and certain secondary amines. The reaction sequence was formally believed to involve a) amine promoted α-elimination of hydrogen fluoride from difluoroamine to yield fluorazene, NF, b) attack of the azene upon the amine, and c) followed by the loss of the elements of hydrogen fluoride. The intermediate formed in the case of the secondary amines would be the corresponding diazene.

When aziridine, azetidine, and dibenzylamine were treated with difluoroamine, nitrogen was evolved and ethylene, cyclopropane, and bibenzyl, respectively, were formed[15]. A more complicated fragmentation of 3,5,5-trimethylpyrazoline occurred when it was treated with difluoroamine. However, the products, acetonitrile, isobutylene, and nitrogen, were certainly consistent with the formation of a diazene intermediate (LVII), whose decomposition may be described formally as shown.


LVII

Bumgardner and coworkers[43] suggested that the diazene intermediate (LX) derived from the reaction of diallylamine (LIX) with difluoroamine was trapped by an internal electrophilic attack upon the double bond. This reasoning, which may or may not be applicable, was based upon the formation of carbazole from o-azidobiphenyl via a nitrene intermediate. A referee also pointed out that the ring closure may have resulted via a diazenium ion, which are known to be highly electrophilic (see sect. III). In view of other previous investigations, two other pathways are conceivable. Both pathways include hydrazone formation, either directly by a process similar to Lemal's or



Urry's or by a cyclic allylic-type rearrangement to an azo compound followed by tautomerism. For example, the phenylhydrazone of acraldehyde was prepared from the alkaline

decomposition of 1-allyl-1-phenyl-2-toluenesulfonylhydrazine, supposedly via the diazene intermediate[38]. Early work by Michaelis[44] gave the isomeric azo compound from the mercuric oxide treatment of 1-allyl-1-phenylhydrazine. It is well known that α,β-unsaturated hydrazones are cyclized to the isomeric pyrazolines[45].

A very interesting reaction[40] of aliphatic secondary amines with Na_2ONNO_2, the so-called Angeli's salt, in acidic media was a convenient source for diazene intermediates. Evidence for this was based upon the marked parallelism with the reaction products obtained by the alkaline decomposition of arenesulfonyl derivatives (see section IV).

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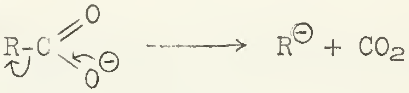
PERFLUOROALKYL AND POLYFLUOROALKYL CARBANIONS

Reported by J. David Angerer October 26, 1964

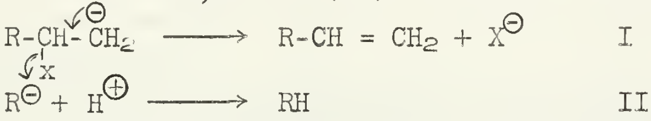
Introduction - Partially - or completely - fluorinated carbanions are suspected intermediates in a variety of reactions: (a) the decarboxylation of alkali metal salts of halo- and perfluoralkylhaloacetic acids, (b) the formation of perfluoroölefins from perfluoroalkyl iodides under the influence of lithium, magnesium and zinc metals, (c) the addition of nucleophiles to perfluoroölefins, and (d) the alkaline hydrolysis of monohydrofluorocarbons and of fluorocarbon halides. It will be the object of this seminar to present evidence concerning the existence of fluorocarbanions as transient species.

The Decarboxylation of Alkali Salts of α-fluorocarboxylic Acids - While the halogen-induced decarboxylation of silver salts of carboxylic acids (the Hunsdiecker reaction) is believed to proceed via a free radical mechanism involving an acyl hypohalite (1), it is generally agreed that the decarboxylation of most alkali metal salts of carboxylic acids proceeds through a carbanionic intermediate:



$$R-C\overset{O}{\underset{O^{\ominus}}{\lessgtr}} \longrightarrow R^{\ominus} + CO_2$$

This carbanionic intermediate may then eliminate a negatively charged atom or group of atoms to form a system that has terminal unsaturation, as in (I), or it may add a proton to become a saturated system, as in (II). Products of both the preceding types have

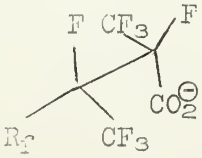


$$R-\underset{X}{CH}-\overset{\ominus}{C}H_2 \longrightarrow R-CH = CH_2 + X^{\ominus} \qquad I$$

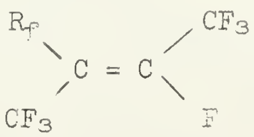
$$R^{\ominus} + H^{\oplus} \longrightarrow RH \qquad II$$

been observed in the case of decarboxylations of perfluorocarboxylic acids (2) (3). Verhoek and coworkers (2) (4) and Johnson and Moelwyn-Hughes (5), working on the decarboxylation of trihaloacetic acids, observed that the rates of decarboxylation of sodium tribromoacetate, sodium trichloroacetate and sodium trifluoroacetate are in the ratio of $10^6 \cdot 10^4 : 1$. In each case, the reaction was discovered to be of first order, depending only upon the concentration of the sodium salt of the acid. The products formed in each case were the corresponding haloforms and carbon dioxide in greater than ninety percent yield. A feature worthy of note is the conditions required for the decarboxylation of the various acids: sodium trifluoroacetate does not decarboxylate at temperatures less than 170°, while sodium trichloroacetate and sodium tribromoacetate decarboxylate readily in boiling water. These conditions may indicate the stability of the carbanions involved, since the formation of the carbanion and carbon dioxide is probably the rate-controlling step, while combination with a proton is very rapid. Thus, one deduces the order of stability for trihalocarbanions to be $CBr_3^{\ominus} > CCl_3^{\ominus} > CF_3^{\ominus}$. This will be discussed more fully later in the seminar.

Hals and coworkers (3) worked with a series of sodium salts of perfluorocarboxylic acids of the type $C_nF_{2n+1}CF_2CF_2CO_2^{\ominus}Na^{\oplus}$, where n = 0,1,2,3,7. They found that, at temperatures of 200-300° and at atmospheric pressure in the absence of solvent, decarboxylation and elimination were taking place to yield a terminal perfluoroölefin, carbon dioxide and sodium fluoride. This is nicely explained by considering a perfluorinated carbanionic intermediate. However, a concerted loss of fluoride and carbon dioxide cannot be discounted at this time since the nature of the products so far obtained tells nothing about the steric course of the reaction. It would be interesting to observe the products of decarboxylation of a perfluorocarboxylic acid such as (III). In the case of a concerted loss of fluoride and carbon dioxide, the olefin (IV) would be expected to form exclusively or preponderently (37). In this seminar, R_f will designate a perfluorinated alkyl group.



III

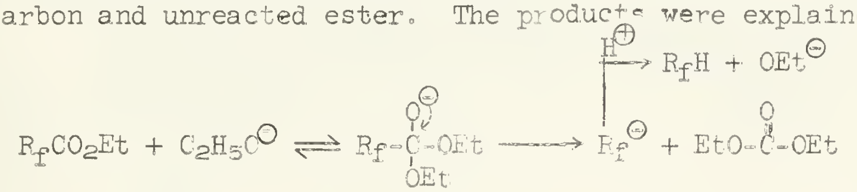


IV

While the decarboxylation of perfluoroalkyl monocarboxylic acids of higher molecular

weight than perfluoroacetic acid yields chiefly terminal perfluoroölefins, the decarboxylation of the ethyl esters of these same acids under the influence of sodium ethoxide yields mainly monohydrofluorocarbons.

Bergman (6) carried out the decarboxylation of the ethyl esters of perfluoroacetic, perfluoropropionic, perfluoro-n-butyric and perfluoro-n-octanoic acids in refluxing ethanol and sodium ethoxide. The observed rates of decarboxylation showed perfluorobutyric and perfluoropropionic acids to be on the order of sixteen times as reactive as perflurooacetic acid. The only observed products in the case of the ethyl esters of perfluoropropionic and perfluorobutyric acids were diethyl carbonate, the corresponding monohydrofluorocarbon and unreacted ester. The products were explained by the following mechanism:



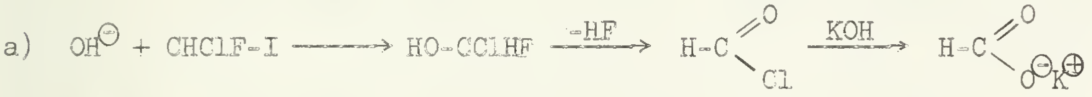
$$R_fCO_2Et + C_2H_5C^{\ominus} \rightleftharpoons R_f-\overset{O^{\ominus}}{\underset{OEt}{C}}-OEt \longrightarrow R_f^{\ominus} + EtO-\overset{O}{\overset{\|}{C}}-OEt \qquad R_f^{\ominus} \xrightarrow{H^{\oplus}} R_fH + OEt^{\ominus}$$

In the case of perfluoroacetic acid, inorganic fluoride was detected, as well as tetrafluoroethylene, diethyl carbonate and fluoroform. The fluoride and tetrafluoroethylene were explained by a decomposition of the trifluoromethyl carbanion to difluorocarbene which subsequently dimerizes.

$$CF_3^{\ominus} \longrightarrow :CF_2 + F^{\ominus} \qquad\qquad 2:CF_2 \longrightarrow CF_2 = CF_2$$

The diethyl carbonate and fluoroform are thought to arise from the normal mode of reaction as proposed above.

Fluorocarbanions from the Attack of Bases Upon Perfluoroalkyl Iodides - Where partially fluorinated methyl and methylene iodides such as $CHFI_2$ and CHClFI decompose to halide and formate when treated with alcoholic potassium hydroxide, it has been observed by Haszeldine (7) that perfluoromethyl iodide, as well as perfluoroalkyl iodides in general, gives the corresponding hydrogeno compound, fluoroform, in good yields under the same conditions. This suggested to Haszelding that two mechanisms could hold: a) a nucleophilic attack on carbon by hydroxyl, which predominates when the compound contains hydrogen and less than two fluorine atoms and b) a nucleophilic attack on iodine or bromine. This is not to say that a rapid reaction involving proton



$$a)\quad OH^{\ominus} + CHClF-I \longrightarrow HO-CClHF \xrightarrow{-HF} H-C\begin{array}{l} /\!\!/ O \\ \backslash\, Cl \end{array} \xrightarrow{KOH} H-C\begin{array}{l} /\!\!/ O \\ \backslash\, O^{\ominus}K^{\oplus} \end{array}$$

$$b)\quad OH^{\ominus} + I-CClF_2 \longrightarrow HOI + {}^{\ominus}CClF_2 \xrightarrow{H^{\oplus}} CHClF_2$$

extraction and hydrogen exchange with solvent is not taking place in a), but this reaction does not lead to products The implications of reaction b) will be discussed later in the seminar.

Increase in the positive character of the iodine will facilitate b) and, as observed, the yield of hydrogeno compound is greatest with perfluoroalkyl iodides.

The formation of ethers during the hydrolysis of perfluoroalkyl iodides other than perfluoromethyl iodide is explained by mechanism d), although this would indicate that isolation of an amount of tetrafluoroethylene might well be observed, where none was reported. In support of this mechanism, it may be noted that a typical addition of ethanol to tetrafluoroethylene requires no heating, but is entirely spontaneous. This may well explain the failure to observe tetrafluoroethylene.

$$OH^{\ominus} + I-CF_2-CF_3 \longrightarrow [{}^{\ominus}CF_2-CF_3] \longrightarrow CF_2 = CF_2 + F^{\ominus}$$
$$CF_2 = CF_2 \xrightarrow{OEt^{\ominus}} [{}^{\ominus}CF_2-CF_2OEt] \xrightarrow{H^{\oplus}} CF_2H-CF_2OEt$$

The iodine in trifluoroiodomethane should have a tendency to behave as if it were positive. Haszeldine and coworkers (8) attempted to show that heterolytic fission of the carbon-iodine bond occurs in polar solutions to yield a fluorocarbanion. Although the conductance of trifluoroiodomethane in the pure state is less than 4×10^{-9} ohms^{-1} at -45°, the authors state that there is probably appreciable ionization in alcoholic solutions of the latter, since they observed that $^{131}I^{-}$ exchanges with the iodine in

trifluoroiodomethane. The reaction was reported to be first order in CF_3I with no dependence on the concentration of iodide. Mason (9) proposed iodine exchange via a complex rather than an intermediate fluorocarbanion. The complex would be of the type $(R_fI^{131}I)^-$, within which the iodine exchanges slowly. Supporting this, Mason has determined the heat of activation of the exchange reaction of perfluoro-n-propyl iodide with radioactive iodide in ethanol to be only 4.2 ± 1.6 kcal./mole. The heat of activation of trifluoromethyl iodide in ethanol was calculated as 3.8 ± 1.9 kcal./mole for the same reaction. The observed $\Delta H^{\ddagger}$ s tend to discount a nucleophilic substitution, for S_N1 or S_N2 reactions of iodine exchange in methyl iodide and other alkyl iodides require a $\Delta H^{\ddagger}$ of 15-25 kcal./mole (10)(11).

RATE DATA ON IODINE EXCHANGE IN PERFLUOROALKYL IODIDES

CF_3I	T(°C.)	$10^{10}k$ (sec^{-1})
	-66	6.2
	-31	16.5
	-5	29
	20	130
	60	176

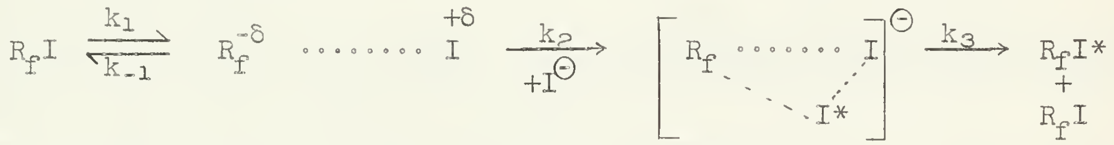
calculated
$\Delta S^{\ddagger} = -84 \pm 7$ e.u.
$\Delta H^{\ddagger} = 3.8 \pm 1.9$ kcal./mole

C_3F_7I	T(°C.)	$10^{10}k$ (sec^{-1})
	-10	0.6
	0	1.0
	25	1.8
	35	2.5
	45	2.7

calculated
$\Delta S^{\ddagger} = -91 \pm 6$ e.u.
$\Delta H^{\ddagger} = 4.2 \pm 1.6$ kcal./mole

The order of the reaction was redetermined and found to be less than 0.5 order in radioactive iodide and between 0.5-1.0 order in trifluoriodomethane. This suggests that two mechanisms or more are at work. Perhaps one of these is the formation of a complex of the type suggested by Mason, but it is not the major route. The heats of activation were recalculated, assuming a second order process, and gave a result that differed by 0.6 kcal./mole from that obtained from an assumption of a first order process.

An alternate mechanism might be the formation of a complex in a manner that would give first order kinetics.



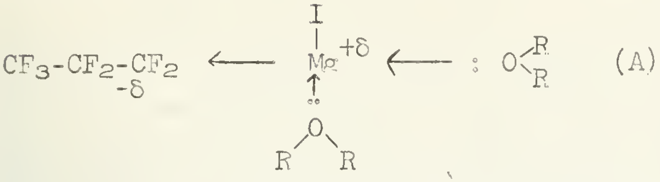
if $k_{-1} < k_2$, first order kinetics would be expected to hold.

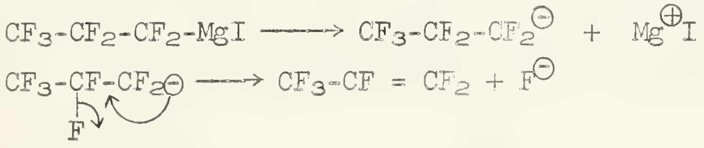
The activation parameters are not explained by any of these mechanisms. The large negative value of $\Delta S^{\ddagger}$, which indicates a highly ordered transition state, and the very low $\Delta H^{\ddagger}$ indicate that no simple process is taking place. There is also the matter of reliability of the data. The author states that the exchange reaction is very susceptible to photochemical free radical reactions. Therefore a small number of free radicals produced from accidental exposure to light could account for the extremely slow reaction observed. Since the reaction was only observed to 0.1% completion, it is unlikely that radioactive trace materials could be identified.

Fluorocarbanions from Fluorocarbon-metallic Compounds - Early attempts (12) to prepare a perfluoroalkyl Grignard reagent failed, probably because of temperatures that were too high for stability of the perfluoroalkylmagnesium. It is to be expected that (A) the carbon-iodine bond is far more polar than the corresponding bond in a hydrocarbon iodide and that (B) a fluorine atom will be lost as fluoride much more readily than hydrogen as hydride. Henne (12), treating polyfluoroalkyl iodides with magnesium in ether at 0°, obtained only gaseous products. Typical of the results was the case of 1,1-difluoro-2-iodoethane. The reaction was extremely vigorous at 0° and yielded a gas shown to be vinyl fluoride. The residue was an equimolar mixture of magnesium iodide and magnesium fluoride.

The first stable perfluoroalkyl Grignard reagent was heptafluoropropylmagnesium iodide, prepared by Haszeldine (13) from heptafluoropropyl iodide and magnesium in diethyl ether, dibutyl ether or dioxane at temperatures of around -30°. The above ethers were chosen because of their properties as good donor solvents, since the carbon-

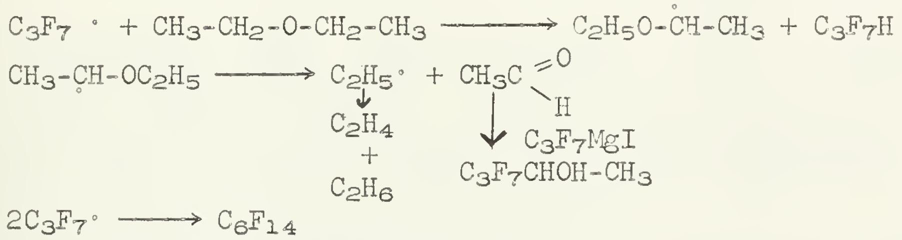
magnesium bond in the perfluoro reagent is more highly polar than that in the corresponding hydrogeno compound. A good donor solvent would be expected to facilitate Grignard formation and stabilization by the formation of complexes as in (A). Products isolated from the decomposition of this Grignard reagent were heptafluoropropane, hexafluoropropene, and a polymer that yielded hexafluoropropene upon pyrolysis. It was suggested by Haszeldine that the hexafluoropropene arose from the elimination of fluoride from the presumed heptafluoropropyl carbanion. This would also explain Henne's results. A concerted mechanism cannot be ruled out. The formation of the polymeric material may be explained by anionic polymerization of hexafluoropropene. The ease of addition of alkoxide ion to the latter, to be discussed later, indicates its susceptability to anionic attack. Use of concentrated solutions of the Grignard reagent led to decomposition that produced heptafluoropropane and other products arising from the solvent. Thus, when acetaldehyde-free ethyl ether was used as solvent, a partially-fluorinated pentanol, ethane, ethylene and acetaldehyde were formed. This is explained by considering a heptafluoropropyl free radical as intermediate The Grignard reagent gave yields of 32-42% of alcohols with acetone, acetaldehyde and formaldehyde.


(A)



$$CF_3\text{-}CF_2\text{-}CF_2\text{-}MgI \longrightarrow CF_3\text{-}CF_2\text{-}CF_2^{\ominus} + Mg^{\oplus}I$$

$$CF_3\text{-}CF\text{-}CF_2^{\ominus} \longrightarrow CF_3\text{-}CF = CF_2 + F^{\ominus}$$



$$C_3F_7\cdot + CH_3\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_3 \longrightarrow C_2H_5O\text{-}\dot{C}H\text{-}CH_3 + C_3F_7H$$

$$CH_3\text{-}\dot{C}H\text{-}OC_2H_5 \longrightarrow C_2H_5\cdot + CH_3CHO$$

$$C_2H_5\cdot \rightarrow C_2H_4 + C_2H_6 \qquad CH_3CHO \xrightarrow{C_3F_7MgI} C_3F_7CHOH\text{-}CH_3$$

$$2C_3F_7\cdot \longrightarrow C_6F_{14}$$

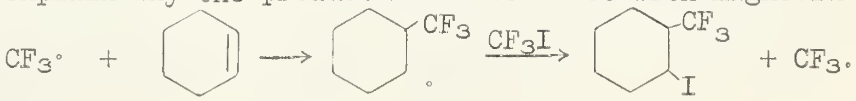
Haszeldine states that the hexafluoropropene observed (15%) probably does not arise from a heptafluoropropyl free radical, because this would give only heptafluoropropane, since loss of fluorine from a free radical would involve homolytic fission of a carbon-fluorine bond and is, therefore, unlikely.

McBee and coworkers (14) prepared perfluoromethylmagnesium bromide in order to check a suggestion by Bergman (6) that difluorocarbene ($:CF_2$) is an intermediate in the decomposition of perfluoromethyl metallics. Bergman suggested that the trifluoromethyl carbanion could lose fluoride ion to become a difluorocarbene, which would dimerize to tetrafluoroethylene, which could easily escape unnoticed through a dry ice-acetone cold trap by virtue of a boiling point of -79°. For this reason, McBee and

$$CF_3^{\ominus} \longrightarrow :CF_2 + F^{\ominus} \qquad\qquad 2:CF_2 \longrightarrow CF_2 = CF_2$$

coworkers carried out the decomposition of trifluoromethyl magnesium bromide in cyclohexene hoping to trap any carbene produced as 7,7-difluorobicyclo (4.1.0)heptane. None of this material was produced, although fluoride ion was detected in the aqueous layer derived from the reaction mixture. The main product of the reaction, and the only product mentioned, was 1-iodo-2-trifluoromethyl cyclohexane, produced in 43% yields. This product cannot be explained using a Grignard reagent as the attacking species. McBee, however, mentioned that the reaction stopped after reaction of only 20-30% of the theoretical amount of the magnesium. This suggests a catalytic role for the magnesium in the addition reaction and also shows there is enough CF_3I present to form the product. Kharasch and coworkers (15) noted that magnesium catalyzed the addition of CCl_3Br to olefins by a free radical process. This suggests the following mechanism for the case of CF_3I. This does not explain why the product fails to react with magnesium.

$$CF_3I + \cdot MgI \longrightarrow CF_3\cdot + MgI_2$$



Perfluoroalkyllithiums are formed by the exchange reactions between perfluoroalkyl iodides and methyllithium, phenyllithium or n-butyllithium. McBee and coworkers (16) observed that perfluoro-n-propyllithium was produced in 97% yield or higher upon treatment of heptafluoropropyl iodide with methyllithium. The yield was based upon the total of the amounts of perfluoropropene and heptafluoropropane isolated after reaction occurred. A control experiment showed no conversion of heptafluoropropyl iodide to either hexafluoropropene or heptafluoropropane, so the products must have arisen from the perfluoroalkyllithium. At 0°, the reagent decomposed without adding to benezophenone; reaction with ethyl perfluoro-n-butyrate yielded 28% of di-perfluoropropyl ketone and 35% hexafluoropropene. An exchange reaction of methyllithium with trifluoromethyl iodide yielded 24% tetrafluoroethylene, presumably arising from a difluorocarbene intermediate. Perfluoro-n-propyllithium reacted with propionaldehyde, acetone and benzaldehyde at temperatures of or below -40° to give addition products:

$C_3F_7CHOHC_2H_5$	50%
$C_3F_7COH(CH_3)_2$	29%
$C_3F_7CHOH-\emptyset$	54%

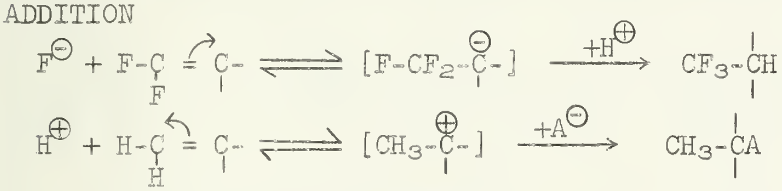
Perfluoroalkylzinc halides were first suspected by Miller (17)(18) who noticed that reduced products were isolated when the dehydrohalogenation of perfluorohalo compounds was attempted. For example perfluoropropylzinc iodide has been formed in yields of 75% by the reaction of perfluoropropyl iodide and zinc at 100°. Hydrolysis of this

$$CF_3-CF_2-CF_2I \xrightarrow[100^\circ]{Zn} [CF_3-CF_2-CF_2^{\ominus}ZnI^{\oplus}] \xrightarrow{H_2O} CF_3-CF_2-CF_2H$$

substance yields heptafluoropropane. Reaction with iodine gave perfluoro-n-propyl iodide. Similar reaction with bromine yielded heptafluoropropyl bromide and heptafluoropropyl iodide, presumably formed by reaction of iodine with the zinc compound. No reaction was observed with carbonyl compounds, but reaction with perfluoro-n-butyryl chloride gave 15% of di-perfluoro-n-propyl ketone.

Fluorocarbanions as Intermediates in the Reactions of Fluoroölefins - Highly fluorinated olefins, in contrast to hydrocarbon olefins, react with anionic and other nucleophiles and tend to resist attack by cationic species. Even such mild nucleophiles as the halides are effective reagents. (19) The differences in the corresponding reactions of fluoroölefins and hydrocarbon olefins are illustrated by the following equations:

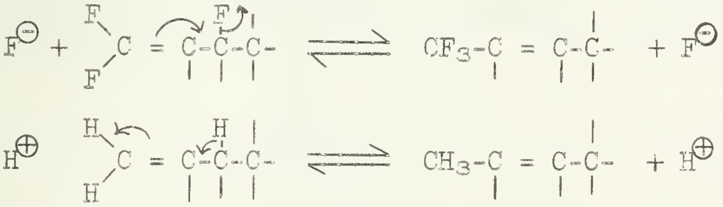
ADDITION



$$F^{\ominus} + F-\underset{F}{C}=C- \rightleftharpoons [F-CF_2-\overset{\ominus}{C}-] \xrightarrow{+H^{\oplus}} CF_3-CH$$

$$H^{\oplus} + H-\underset{H}{C}=C- \rightleftharpoons [CH_3-\overset{\oplus}{C}-] \xrightarrow{+A^{\ominus}} CH_3-CA$$

SUBSTITUTION WITH REARRANGEMENT



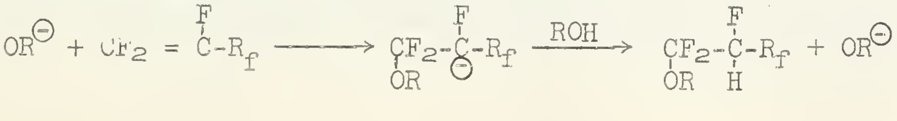
$$F^{\ominus} + F_2C=C-\overset{F}{C}-C- \rightleftharpoons CF_3-C=C-C- + F^{\ominus}$$

$$H^{\oplus}\quad H_2C=C-\overset{H}{C}-C- \rightleftharpoons CH_3-C=C-C- + H^{\oplus}$$

These are the two principal reactions of the fluoroölefins. It is understood that $F^{\ominus}$ may be replaced by another nucleophile in the above illustration.

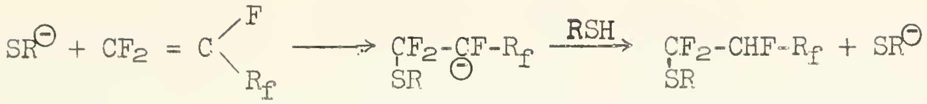
Among the reagents which add to fluoroölefins are alcohols (20)(21)(22)(23)(24)(25), mercaptans (25)(26), phenols (24)(27), Grignard reagents (28), ketoximes (25)(29), primary and secondary amines (25)(30) and carbonyl fluoride (31). Generalized schemes are illustrated below.

A.



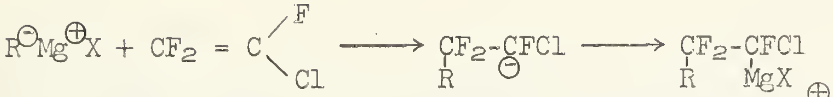
$$OR^{\ominus} + CF_2=\overset{F}{C}-R_f \longrightarrow \underset{OR}{CF_2}-\overset{F}{\underset{\ominus}{C}}-R_f \xrightarrow{ROH} \underset{OR}{CF_2}-\overset{F}{\underset{H}{C}}-R_f + OR^{\ominus}$$

B.



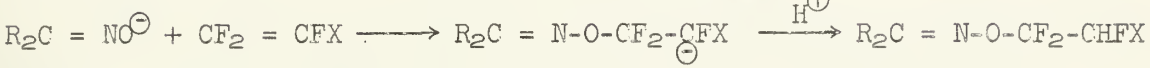
$$SR^{\ominus} + CF_2=C\begin{matrix}F\\R_f\end{matrix} \longrightarrow \underset{SR}{CF_2}-\underset{\ominus}{CF}-R_f \xrightarrow{RSH} \underset{SR}{CF_2}-CHF-R_f + SR^{\ominus}$$

C.



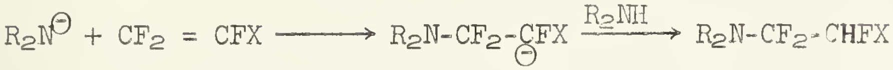
$$R^{\ominus}Mg^{\oplus}X + CF_2=C\begin{matrix}F\\Cl\end{matrix} \longrightarrow \underset{R}{CF_2}-\underset{\ominus}{CFCl} \longrightarrow \underset{R}{CF_2}-\underset{MgX}{CFCl}$$

D.



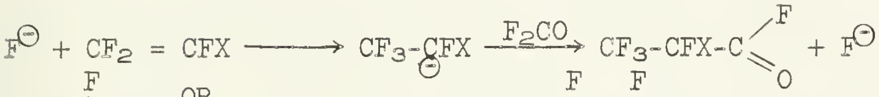
$$R_2C=NO^{\ominus} + CF_2=CFX \longrightarrow R_2C=N-O-CF_2-\underset{\ominus}{CFX} \xrightarrow{H^{\oplus}} R_2C=N-O-CF_2-CHFX$$

E.



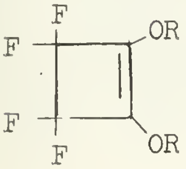
$$R_2N^{\ominus} + CF_2=CFX \longrightarrow R_2N-CF_2-\underset{\ominus}{CFX} \xrightarrow{R_2NH} R_2N-CF_2-CHFX$$

F.

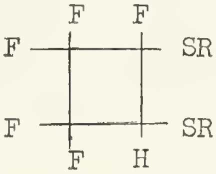


$$F^{\ominus} + CF_2=CFX \longrightarrow CF_3-\underset{\ominus}{CFX} \xrightarrow{F_2CO} CF_3-CFX-C\begin{matrix}F\\O\end{matrix} + F^{\ominus}$$

G.

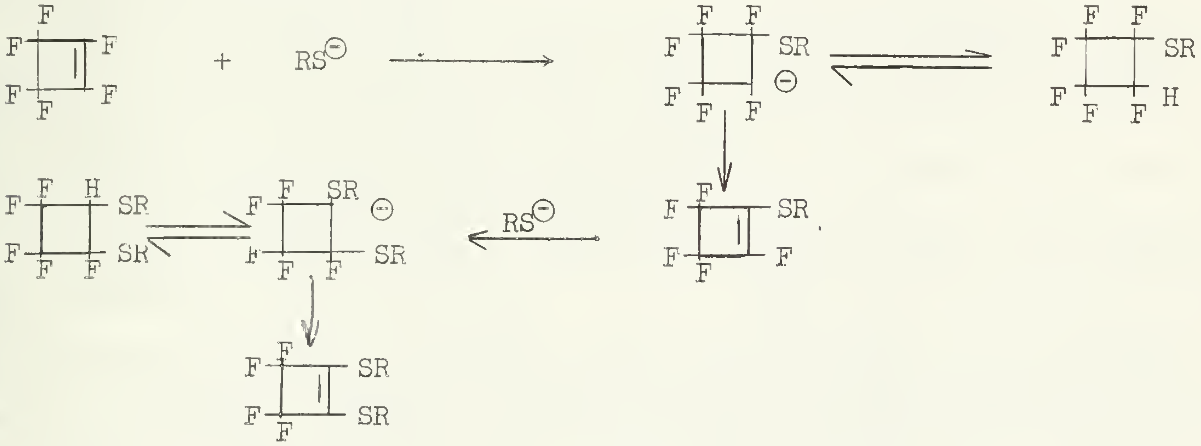


H.

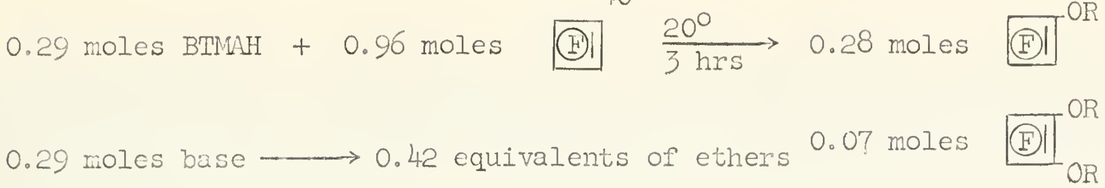


A fluoroölefin that has been most extensively studied with respect to nucleophilic attack is perfluorocyclobutene. The first work performed was by Park and coworkers (23). They observed that only unsaturated ethers of the form (G) were produced by the action of alkoxide on perfluorocyclobutene. In a typical reaction, hexafluorocyclobutene was bubbled through a solution of 10% potassium hydroxide in the alcohol at room temperature. The reaction was quenched and the product washed with water, dried over calcium oxide and fractionated under reduced pressure. Yields of 1,2-dialkoxy-3,3,4,4-tetrafluorocyclobutenes ranged from 56%-75%. The products were identified by permanganate oxidation of the olefin to a diester derivative of tetrafluorosuccinic acid. The saponification product was also checked and found to be tetrafluorosuccinic acid. On the basis of this evidence, Park postulated a vinylic substitution process, much like that of phenoxide with halobenzenes.

However, Rapp and coworkers (26), investigating the corresponding reaction with mercaptans, isolated a saturated disulfide of the type (H) which evolved hydrogen fluoride upon distillation and evolved large quantities of hydrogen fluoride upon standing overnight. This led Rapp to propose an addition-elimination mechanism for the reaction. The only way a product such as (H) could arise from vinylic substitution



would be by adding hydrogen fluoride across the double bond. This is discounted for the reason that hydrogen fluoride is actually evolved from the compound. This led Barr (24) to reinvestigate Park's work. Although he and his coworkers could not isolate alkoxy compounds corresponding to (H), they did notice considerable quantities of hydrogen fluoride being given off during distillation. They also observed in cases where benzyltrimethylammonium hydroxide (BTMAH) was used that more moles of ethers were produced than there were moles of base present during the reaction. Some typical results are listed below. This would require one of the two following processes: (1) substi-



$$0.29 \text{ moles BTMAH} + 0.96 \text{ moles } \boxed{F} \xrightarrow[3 \text{ hrs}]{20^{\circ}} 0.28 \text{ moles } \boxed{F}\text{-OR}$$

$$0.29 \text{ moles base} \longrightarrow 0.42 \text{ equivalents of ethers} \quad 0.07 \text{ moles } \boxed{F}(\text{OR})_2$$

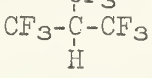
tution took place after the neutralization of the base, or (2) reaction was one of addition, and subsequent loss of hydrogen fluoride neutralized the catalyst and stopped the reaction. The latter seems more probable in view of the fact that no reactions of polyfluoro olefins with alkoxy groups under acid of neutral conditions have been reported. This would also account for the hydrogen fluoride produced upon purification.

Carbanions as Intermediates in the Reaction of Haloforms and Monohydrofluorocarbons with Base - Andreades (32) has studied the acidities of monohydrofluorocarbons bearing hydrogen in primary, secondary and tertiary positions by carrying out exchange reactions in sodium methoxide-methanol-O-d solution. Compounds studied were fluoroform (I), 1-H-pentadecafluoroheptane (II), 2-H-heptafluoropropane (III), and tris(trifluoromethyl) methane (IV). It was found that the relative reactivities of I-IV were 1.0 : 6 : 2 x 10^5 : 10^9, indicating increasing stability in the series of carbanions, in the order $1^{\circ} < 2^{\circ} < 3^{\circ}$. This indicates that β-fluorine is more stabilizing than α-fluorine, which may be rationalized by hyperconjugative resonance. This would allow nine, six and two fluorine atoms to participate in stabilization of IV, III and II, respectively, accounting for the stability order observed.

CF_3H I

$CF_3(CF_2)_5CF_2H$ II

$CF_3\text{-}CHF\text{-}CF_3$ III



$CF_3\text{-}\overset{CF_3}{\underset{H}{C}}\text{-}CF_3$ IV

An elimination-addition mechanism for the exchange reaction was ruled out, since in the exchange of 1-H-pentadecafluoroheptane (II) none of the 2-H isomer was produced, judged by n.m.r. and mass spectral analysis. This product would be expected if an intermediate perfluoroheptene were produced, since fluoride has been observed to add to the terminal CF_2 = group. (19)

Mass spectral analysis was used as the most convenient method of analysis of isotopic mixtures of monohydrofluorocarbons. For example, analysis of (I) gave peaks at m/e 51-52 which correspond to the ions CHF_2^+ and CDF_2^+, respectively, and yielded relative percentages of the isomers after the peak at m/e 52 was corrected for the natural abundance of C^{13} in CHF_2^+.

Since elimination-addition has been discounted as the mechanism of exchange and no evidence for a single-step, base catalyzed exchange reaction of a carbon bound hydrogen has ever been substantiated (33), there seems to be little doubt that a carbanionic species is responsible for the exchange.

Perhaps the greatest insight into trihalocarbanion stability is afforded by a study of the exchange reactions of haloforms.

It is the consensus of opinion that the hydrogen exchange of haloforms takes place through a trihalocarbanion. The proton abstraction is the rate-determining step,

$$CHX_3 + OD^{\ominus} \rightleftharpoons CX_3^{\ominus} + HOD \quad (\text{slow}) \qquad CX_3^{\ominus} + D_2O \longrightarrow CDX_3 + OD^{\ominus} \quad (\text{fast})$$

so the rate of exchange is a measure of the rate of formation of the carbanion and, since a more stable carbanion is formed more rapidly than a less stable one, a direct measure of carbanion stability. Studies by Hine and coworkers (34) have shown carbanion formation in the haloform series to be favored in the order I ~ Br > Cl > F.

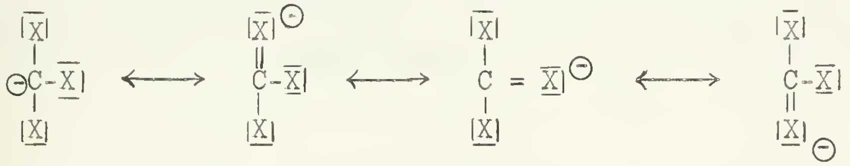
EXCHANGE RATES OF HALOFORMS IN 66 2/3% AQUEOUS DIOXANE

HALOFORM	k (1.mole^{-1}sec.$^{-1}$) at 0°
CDI_3	60.1×10^{-2}
$CDBr_3$	57.9×10^{-2}
$CDCl_3$	47.0×10^{-4}
$CDFCl_2$	0.89×10^{-4}
CDF_3	$< 10^{-6}$

Before this study, the ease of formation of the carbanion from chloroform had been attributed to the electronegativity of the chlorine atoms, but the data show other forces at work. There are apparently three factors to be considered in explaining why the rates of carbanion formation are the reverse of that to be expected from the inductive effect.

One factor is "B-strain", a term originated by Brown (35)(36) to designate repulsions between the three halogen atoms of the tetrahedral haloform. Such repulsions are eased by the formation of the more nearly planar carbanion. However, steric effects should increase quickly once they are a factor, but, although there are increases in the reactivity in changing fluorine to chlorine and chlorine to bromine, there is no corresponding increase when bromine is changed to iodine.

A second factor that may be considered is "d-orbital resonance", by which trihalomethyl carbanions may be stabilized by the contribution of structures having ten electrons in the outer shell of a halogen atom. Fluorine is the only halogen that is unable to expand its outer shell to ten electrons.



Since decreasing electronegativity in a given row of the periodic chart is associated with increasing covalent radius, the order $Cl > Br > I > F$ should be obtained if d-orbital resonance is important but constant for the three heavier halogens.

The third factor is polarizability. The largest change in polarizability is between fluorine ($.96 \times 10^{-24} cm^3$) and chlorine ($3.60 \times 10^{-24} cm^3$). Smaller percentage increases are found upon going to bromine ($5.0 \times 10^{-24} cm^3$) and iodine ($7.60 \times 10^{-24} cm^3$). This would put the order of reactivity in the observed order.

Summary - Evidence has been collated supporting the idea of fluorocarbanions as transient species and reflecting upon their stabilities relative to other halocarbanions.

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FREE RADICAL ADDITIONS TO ALLENES

Reported by Raymond Feldt October 29, 1964

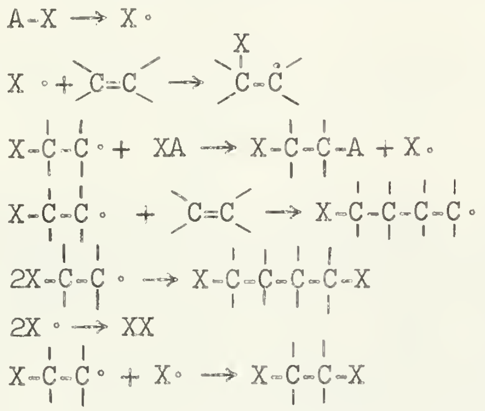
Introduction - A very useful method of synthesis is the radical addition of various reagents to carbon-carbon double bonds in olefins. The use of this method to prepare new carbon-carbon (1) or carbon-heteroatom (2) bonds has been reviewed. Other reviews on radical reactions and rearrangements have also been published recently (3,4).

The cumulenes are a unique series of olefins of the general structure I, where n is 1 or larger.

$$R_2C \mathbin{\neq} C \mathbin{\neq}_n CR_2 \qquad \text{I}$$

The simplest members of this series are the allenes, n = 1. Reviews concerning the synthesis of allenes and cumulenes in general have appeared recently (5,6,7). This seminar will be limited to radical additions to allenes. Radical additions to allene are of interest in themselves and as a source of difunctional intermediates for further reaction.

Orientation in radical additions to olefins - The generally accepted reaction sequence for radical additions to olefins is the following:



Initiation: $A{-}X \rightarrow X\cdot$ (1)

Addition: $X\cdot + \rangle C{=}C\langle \rightarrow \rangle\overset{X}{\overset{|}{C}}{-}\dot{C}\langle$ (2)

Chain transfer: $X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\cdot + XA \rightarrow X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}A + X\cdot$ (3)

Progagation: $X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\cdot + \rangle C{=}C\langle \rightarrow X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\cdot$ (4)

$2X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\cdot \rightarrow X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}X$ (5)

Termination: $2X\cdot \rightarrow XX$ (6)

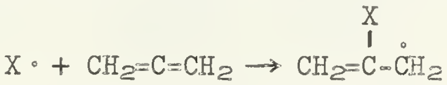
$X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\cdot + X\cdot \rightarrow X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}X$ (7)

In the reactions to be discussed here the chain transfer step predominates over the propagation step.

In the addition step (eq. 2) to unsymmetrically substituted olefins the product is usually the "abnormal" or anti-Markownikoff product. This means that the orientation of the added reagent is the reverse of that for an electrophilic substitution.

Present evidence indicates that the orientation can be correlated well with the stability of the intermediate radical (4) and assuming that the product is derived from the most stable radical. In general, radical stability parallels carbonium ion stability. Thus tertiary radicals are more stable than secondary radicals which are more stable than primary radicals. The actual order of a given pair of radicals will be determined by the atoms or groups attached to the radical site. For example, the following order of stabilizing ability was found for some atoms: H $<$ F $<$ Cl. Formation of a benzyl or allyl radical which can be stabilized by resonance also may influence the actual stability order and therefore orientation of addition.

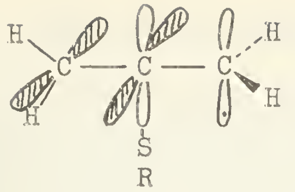
On this basis, it would appear that radical additions to allene should proceed with initial attack on the center carbon to give the more stable allylic radical intermediate (eq. 8).



$$X\cdot + CH_2{=}C{=}CH_2 \rightarrow CH_2{=}\overset{X}{\overset{|}{C}}{-}\dot{C}H_2 \qquad (8)$$

This should also hold if the allene were symmetrically substituted as in 2,3-pentadiene.

There is some question whether the radical should be considered an allylic one. Due to the geometry of the allene system, II, the orbital containing the radical is perpendicular to the π bond of the double bond. Therefore, the radical formed resembles a primary radical since effective overlap is prevented unless rotation occurs. Because of the lack of overlap, the activation energy for center attack may be larger than for terminal attack (8,9).



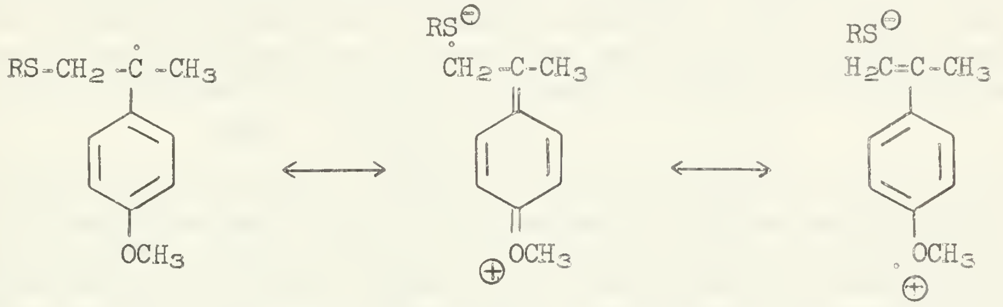
II

Orientation may also be affected by steric effects (1). It is known that non-terminal double bonds are less reactive than terminal olefins and that a radical usually adds to the less substituted end of a double bond. It should be pointed out that this orientation will usually give the most stable intermediate radical.

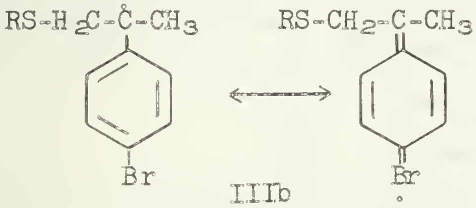
It is now felt that polar effects may be important in radical additions (2). It has been found that in the competitive addition of mercaptoacetic acid to para- substituted α-methylstyrenes (28), the relative rates of addition decreased in the following order,

$$CH_3O > CH_3 > H > Br > F$$

with the relative rates being; 215: 2.28: 1: 0.90: 0.51 respectively. The rate enhancement by CH_3O was interpreted to mean that resonance forms such as IIIa contribute to the intermediate radical. If these resonance forms are important, rates of addition and possibly orientation would be affected by the relative electrophilicity or nucleophilicity of the attacking radical and of the substrate. For example, the addition of a series of radicals, ranging from strongly electrophilic to strongly nucleophilic, to a substance may result in a change in the attack site.



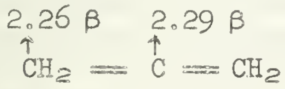
IIIa



IIIb

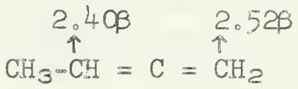
The general trend in the series above is toward slower reaction with an increase in the electron-withdrawing ability of the substituent which is consistent with resonance forms such as IIIa. However, it is not known to what extent forms such as IIIb, in which no charge separation is present, contribute. The study of the para-NO_2 and para-I compounds and the reaction of CH_3 radicals, which are considered to be nucleophilic rather than electrophilic as are thiyl radicals, with the same series would be of interest.

Molecular orbital calculations of radical localization energies, given in β units, have also been used to predict the site of radical attack. Pullman (10) has carried out these calculations of the differences in π energy of the molecule before and after addition of a radical for allene (IV) and 1,2-butadiene (V). The lower localization energies for the terminal carbons in IV, (2.26 β), and C-3 in V, (2.40 β), are apparently attributed to hyperconjugation of the hydrogens and the methyl group. However the parameters necessary to carry out the calculations were not reported. The authors concluded that radicals would preferentially attack at the site with the lowest localization energy. Thus terminal attack on allene and attack at C-3 in 1,2-butadiene should predominate.



$$\overset{2.26\,\beta}{\overset{\uparrow}{CH_2}} = \overset{2.29\,\beta}{\overset{\uparrow}{C}} = CH_2$$

IV

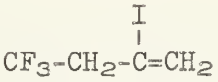


$$CH_3\text{-}CH = \overset{2.40\beta}{\overset{\uparrow}{C}} = \overset{2.52\beta}{\overset{\uparrow}{CH_2}}$$

V

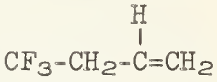
Addition of methyl and trifluoro methyl radicals - Haszeldine and co-workers reported the first addition of CF_3 radicals to allene (11). They allowed CF_3 I to react with allene in a sealed silica tube and irradiated for 48 hours with ultraviolet light. Products with a boiling point greater than 0° were isolated in 32% yield. The product mixture was concluded to contain 96% 4,4,4-trifluoro-2-iodobut-1-ene (VI) since the U.V. spectrum was nearly identical to that of 4,4,4-trifluoro-2-iodobut-2-ene, which

also contains the $-CH_2-\underset{I}{C}=CH_2$ system, and quite different from the spectrum of allyl iodide which should be analogous to the product resulting from addition of the CF_3 radical to the center carbon of the allene system. Infrared spectra showed C=C absorption at 6.17 μ, which is characteristic of vinylic iodides, and strong absorption for a terminal methylene at 10.93 μ, which was shifted from 11.24 μ in unsubstituted olefins. VI was also dehalogenated to 4,4,4-trifluoro-but-1-ene, VII, with Zn and acid. VII was identified by I.R. spectra and an independent synthesis of VII. The remaining 4% of the product was higher boiling material which was not identified. The products indicate that terminal attack occurred at least 96% of the time.



$CF_3-CH_2-\overset{I}{C}=CH_2$

VI



$CF_3-CH_2-\overset{H}{C}=CH_2$

VII

Szwarc and co-workers have studied the addition of CH_3 and CF_3 radicals to allenes in either isooctane or toluene solution. They developed a method of determining the relative rates of addition of these radicals to various aromatic and olefinic compounds.

When the thermal decomposition of acetyl peroxide, to give methyl radicals (12), is carried out in dilute solutions in isooctane, the products are CO_2, CH_4 and C_2H_6, which follow the stoichiometric relation in equation 9. Since the relationship is 1,

$$([CH_4] + 2[C_2H_6])/[CO_2] = 1 \qquad (9)$$

it was concluded that the solvent radicals produced to not react with the methyl radicals under the conditions used here. This indicates that the probability of a solvent radical combining with a methyl radical is very small. Thus the stationary concentration of solvent radicals is larger than that of methyl radicals and the solvent radicals eventually react in pairs. The addition of an aromatic compound to such a reaction mixture decreases the amount of methane formed but does not affect the amount of ethane or CO_2. Since the stationary concentration of intermediate radicals was low, it was concluded by analogy to the situation with solvent radicals that the radicals produced by addition of a CH_3 radical to an aromatic compound did not react further with methyl radicals. This indicates that two reactions are possible for methyl radicals (eq. 10, 11). It appears that reaction 11 is responsible for the decrease in

$$CH_3\cdot + \text{iso-octane} \longrightarrow CH_4 + \text{iso-}C_8H_{17}\cdot \qquad (10)$$

$$CH_3\cdot + \text{aromatic} \longrightarrow CH_3\cdot\text{aromatic} \qquad (11)$$

number of methyl radicals converted into methane in the presence of an aromatic compound. Letting k_{10} and k_{11} denote the bimolecular rate constants for reaction 10 and 11, the authors conclude that equation 12 expresses the rate of addition to the aromatic compound relative to the rate of hydrogen abstraction from the solvent. The term $(CH_4/CO_2)_{solvent}$ is a constant giving the ratio of the amounts of these two products formed in pure isooctane and $(CH_4/CO_2)_{ar}$ denotes the ratio when an aromatic compound is present and X refers to the mole fraction of the substances present.

$$\frac{k_{11}}{k_{10}} = \left([(CH_4/CO_2)_{solvent} - (CH_4/CO_2)_{ar}] / (CH_4/CO_2)_{ar}\right) \times (X_{C_8H_{18}}/X_{aromatic}) \qquad (12)$$

Equation 12 holds only if the mole fractions of isooctane and of the aromatic compound remain constant throughout the run. This is essentially true if only a small fraction of the aromatic compound reacts with methyl radicals. Since the concentration of the peroxide was near 10^{-2} mmoles/cc, equation 12 holds for aromatic concentrations of not less than 10^{-1} mmoles/cc and if the fraction of decomposition of the peroxide is small.

Hydrogen abstraction from the aromatic compound by the methyl radicals provides a second route for CH_4 production thus causing equation 12 to give erroneous k_{11}/k_{10}. The authors concluded that if the k_{11}/k_{10} ratio was constant as the concentration of the aromatic compound varied hydrogen abstraction was not important. This was shown to be true for allene.

Using the above method, Szwarc and co-workers (15) studied the addition of methyl

radicals to conjugated olefins and allenes. The olefin samples were dissolved in isooctane, acetyl peroxide added and then the solutions were deaerated. The samples were sealed in tubes and placed in thermostated baths. Analysis of products was done in a vacuum apparatus. The amounts of CO_2, CH_4 and ethane were obtained by fractional distillation of the reaction mixture. The ratio k_{11}/k_{10} was then calculated from the product yields.

Szwarc's results on conjugated dienes indicated that groups on the terminal carbons of the conjugated system exert a strong steric effect which lowers reactivity. For example, the rate of reaction of 2,4-hexadiene with methyl radicals is lower by a factor of 11 than that of 1,3-butadiene. From results on a series of olefins, it was concluded that substitution of one methyl group on the terminal carbon would lower the reactivity toward methyl radicals by a factor of 9 ± 2 and 2 methyls would lower reactivity about 100 times. If phenyl groups replace the methyls, reactivity is lowered by a factor of 5 and 34, respectively, compared to 1,3-butadiene. These results and the fact that 2,3-dimethyl-1,3-butadiene has nearly the same k_{11}/k_{10} as the unsubstituted compound indicate that attack is on the terminal carbon.

Table I

Relative Rates of Addition of Methyl Radicals to Allenes

Compound	Temperature	k_{11}/k_{10}	Range of concentration (mole %)
allene	55	20.3 ± 0.2	3.4 → 6.3
	65	17.6 ± 0.2	" "
	75.2	16.0 ± 0.2	" "
	85	14.3 ± 0.2	" "
1,2-butadiene	55	17.2 ± 1	2.2 → 8.8
	65	14.8 ± 2	2.9 → 7.4
	75.2	13.4 ± 1	2.0 → 9.2
	85	13.5 ± 1	2.2 → 6.5
1,2-pentadiene	65	19.2	1.4 → 5.0
2,3-pentadiene	65	13.8	1.3 → 4.8
tetraphenylallene	65	52	1.5 → 2.9

Since an alkyl or phenyl substituent on the terminal carbon of allene does not decrease the reactivity significantly (Table I) and since the blocking effect of such substituents is known, Szwarc concluded that the center carbon of the allene system is the site of attack. This mode of attack would also give the more stable intermediate radical if there were any overlap between the radical orbital and the π system of the double bond. There also is the possibility that the site of attack varies with the allene. Attack may be mainly on the terminal carbon for allene itself and gradually shift to the center carbon with increased substitution. The methyl affinities are not inconsistent with this view (9).

The addition of CF_3 radicals to olefins and allenes was also studied by Szwarc and co-workers (16). The method employed was similar to that used for addition of methyl radicals. The CF_3 radicals were produced in isooctane solution by photolysis of hexafluoroazomethane at 65°. The only products were CF_3H, C_2F_6 and N_2 when no olefin was added to the solution. The ratios CF_3H/N_2 and $2\ C_2F_6/N_2$ were found to be constant and independent of concentration and their sum $(CF_3H + 2\ C_2F_6)/N_2 = 2 \pm 0.03$. The addition of olefins reduced the CF_3H/N_2 ratio but did not affect the C_2F_6/N_2 ratio. The relative rates were reported as k_{11}/k_{10} ratios with the appropriate fluorocompound replacing the hydrogen compound. In these experiments, analysis of the reaction products was done by v.p.c. on a silica gel column.

Table II

Relative Rates of Addition of CF_3 Radicals to Olefins at 65°

Compound	Concentration range (mole fraction x 10^3)	k_{11}/k_{10}
$CH_2=C=CH_2$	1.2 → 4.2	299 ± 9
$CH_2=C=CH_2$	1.1 → 5.0	283 ± 20
$CH_3-CH=C=CH-CH_3$	1.6 → 5.0	413
$CF_2=CF_2$	3.2 → 11.5	68.6 ± 42

Szwarc concludes from these data, that the CF_3 radical is more reactive than the CH_3 radical. This conclusion was based on the assumption that CF_3 radicals abstract hydrogen from the solvent faster than do methyl radicals. However, the data indicate that the CF_3 radical reacts more selectively with the aromatic compound over the solvent than does the CH_3 radical. On this basis, the CF_3 radical appears to be less reactive than the methyl radical.

Szwarc and co-workers concluded that if CF_3 radicals add to the terminal position of allene, as reported by Haszeldine, 2,3-pentadiene would be expected to be more reactive than allene analogous to the pair ethylene:2-butene. The electron donating ability of the methyl groups increases the electron density on the terminal carbons of the allene system. Since the CF_3 radical is strongly electrophilic, it attacks preferentially at the terminal site. The rate increase due to increased electron density is large enough to overcome the rate decrease caused by steric hindrance. The increase in electron density should lower the reactivity of 2,3-pentadiene toward CH_3 radicals if addition is at the terminal carbons. Since there was almost no rate lowering, Szwarc concluded that CH_3 radicals attack the center carbon in allenes. It should be pointed out that Szwarc and co-workers did not isolate and identify any of their addition products.

It had been assumed that the addition of CH_3 and CF_3 radicals was not reversible. Szwarc and co-workers (17) have concluded that if reversibility were significant, the ratio k_{11}/k_{10} would vary as the concentration of the azo compound varied. Since k_{11}/k_{10} ratios remained constant, reversibility was concluded to be unimportant. This is supported by the fact that no isomerization of cis- or trans-dichloroethylene, recovered from an addition reaction, could be detected by v.p.c. analysis. Similar results have been obtained for the addition of CCl_3 radicals to cis- and trans-2-butene (18).

Although these additions appear to be irreversible on olefins, this has not been explicitly shown on allenes. Isomerization experiments, starting with optically active allenes, should provide the information. If the radical addition is reversible, the recovered allene should show some racemization.

Thiol additions to Allene - The radical additions of thiols to allenes to yield alkyl sulfides have received a great deal of attention, with the additions to allene itself receiving the most. Griesbaum and Oswald (19) have studied the addition of H_2S to allene with varying allene to thiol ratios. The experiments were carried out by condensing H_2S and allene into a quartz tube at -70 to -80°. Initiation was by a combination of 2,2'-azobis-isobutyronitrile (AIBN) or t-butyl hydroperoxide and ultraviolet light irradiation. The reaction mixtures were irradiated for 24 hours, the unreacted H_2S and allene were allowed to distill off, and the product mixtures left behind were analyzed by v.p.c., time of flight mass spectrometry, n.m.r. and I.R.

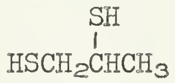
When an excess of H_2S was allowed to react with allene, 90-95% of the product mixture was 1,3-propanedithiol (IX), and 3-propenethiol (X) in varying relative amounts depending on the ratio of the starting materials. Of the remainder, 1-2% was identified as 1,2-propanedithiol (XI) but no 2-propenethiol (XII) was detected. Since it is assumed in all the radical additions of thiols that the initial attack is by the thiyl radical (RS·) with subsequent hydrogen abstraction from a second thiol molecule, the authors concluded that the amount of IX and X represented the amount of terminal attack on allene.

$HS{-}CH_2CH_2CH_2{-}SH$

IX

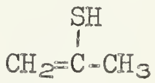
$H_2C{=}CH{-}CH_2{-}SH$

X



$HSCH_2CH(SH)CH_3$

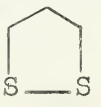
XI



$CH_2{=}C(SH){-}CH_3$

XII

It was assumed that XI resulted from initial attack on the center carbon of allene, but XI could also result from addition to X. Reactions of equimolar amounts of H_2S and allene gave IX and X as 65% of the products with approximately 10% each of trimethylenedisulfide (XIII), allyl(3-mercaptopropyl)sulfide (XIV), and bis(3-mercaptopropyl)-sulfide (XV).



XIII

$CH_2{=}CHCH_2S(CH_2)_3SH$

XIV

$HS(CH_2)_3S(CH_2)_3SH$

XV

The radical addition of methanethiol to allene has been studied by Griesbaum and Oswald (8) and the addition of ethanethiol by Jacobs and Illingworth (9). The reactions were carried out with the allene and thiol ratio between 1 and 3. All the reactions were run in quartz tubes which were filled at -78° and then sealed. The additions of methanethiol were initiated by t-butyl hydroperoxide and ultraviolet light at various temperatures and the ethanethiol additions were initiated by AIBN at 67° with no U.V. irradiation. The resulting product mixtures were analyzed by v.p.c., n.m.r., and I.R.

The free radical nature of the additions was shown explicitly for the addition of methanethiol by following the disappearance of thiol in runs with no initiator present, with only U.V. light, and with a combination of peroxide and U.V. initiation. The relative rates were 1:5.5:7.5, respectively.

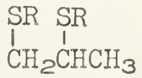
In both methane- and ethanethiol additions to allene, the major products were the monoadducts resulting from addition of the thiyl radical to the terminal carbon, allyl methyl sulfide (XVI) and allyl ethyl sulfide (XVII), respectively; the 1,3-diadducts, 1,3-dimethylthiopropane (XVIII) and 1,3-diethylthiopropane (XIX), respectively; and the 1,2-diadducts, 1,2-dimethylthiopropane (XX) and 1,2-diethylthiopropane (XXI). In both cases, no 2-methylthiopropene (XXII) or 2-ethylthiopropene (XXIII), corresponding to addition of the thiyl radical to the center carbon, was detected. This was not surprising since it has been shown (20) that XXIII is very reactive toward ethanethiyl radicals and readily forms the 1,2-addition product.

$CH_2{=}CH{-}CH_2{-}S{-}R$

XVI, R = CH_3
XVII, R = CH_3CH_2

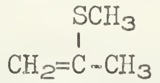
$RS{-}CH_2{-}CH_2{-}CH_2{-}SR$

XVIII, R = CH_3
XIX, R = CH_3CH_2



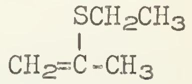
$\overset{SR}{CH_2}\overset{SR}{CH}CH_3$

XX, R = CH_3
XXI, R = CH_3CH_2



$CH_2{=}\overset{SCH_3}{C}{-}CH_3$

XXII



$CH_2{=}\overset{SCH_2CH_3}{C}{-}CH_3$

XXIII

There are several possible routes by which the 1,2-diadducts may be formed. Their formation by addition of thiol to methylacetylene formed by isomerization of allene was ruled out since no methylacetylene could be detected in the unreacted allene by v.p.c. analysis. It was shown in a competitive addition of methanethiol to an equimolar mixture of allene and methylacetylene that the addition rates are nearly equal. This result was supported by the absence of cis- and trans-1-ethylthio-1-propene in the reaction products. These had been shown to form when ethanethiol was added to methylacetylene.

The possible formation of the 1,2-diadduct from either XVI or XVII seemed unlikely since it is known that thiyl radicals attack the terminal carbons of olefins almost exclusively (4, 21). This was substantiated for the addition of methanethiol to XVI under the same conditions as the addition to allene. The product was found to be 7% the 1,2-diadduct, XX. Thus it was concluded that at least 93% of the 1,2-diadduct formed resulted from initial attack on the center carbon. It was found that changes in temperature resulted in changes in the amount of center attack.

Griesbaum and co-workers (8) have studied the additions of benzenethiol and thiolacetic acid to allene under the reaction conditions described above. In both cases, the monoadduct resulting from terminal addition of the thiyl radical amounted to 70% of the identified products. The 1,3-diadduct made up 10% of the product from benzenethiol addition and 18% in the thiolacetic acid addition. The 1,2-diadduct, which was assumed to represent the amount of initial attack on the center carbon, made up 13% of the benzenethiol addition and 9% in the thiol acetic acid additions.

Jacobs and Illingworth (9) were able to isolate and identify only the monoadduct in 50% yield when benzenethiol was added to allene using AIBN initiation. Since the reaction product did not react with 2,4-dinitrophenylhydrazine reagent, indicating that phenylisopropenyl sulfide, the result of addition to the center carbon, was absent, it was concluded that center attack had not occurred. In view of the absence of the monoadduct in other thiol additions to allene and the fact that others are known to be extremely reactive, it is possible that some center attack did take place and the resulting product reacted with more of the thiol or allene to give the unidentified products.

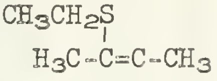
While most of the studies on allene were carried out without an added solvent, van der Ploeg and co-workers (22) have carried out the addition of propane-, benzene-, and α-toluenethiol to allene in benzene solution. The reaction was initiated with AIBN and heated at 82° for 4 hours. Analysis by n.m.r. and I.R. indicated that the amount of 1,2-diadduct formed was higher than in additions which were not run in a solvent and that when benzenethiol was added with a high allene: thiol ratio, some monoadduct corresponding to center addition was isolated. The 1,3-diadducts were not detected in the additions of propane- and α-toluenethiol to allene.

Thiol additions to substituted Allenes - Radical additions of ethane- and benzenethiol to two substituted allenes, 1,2-butadiene and 3-methyl-1,2-butadiene, have been studied by Jacobs and Illingworth (9) using initiation with AIBN and heat as for addition to allene. Product mixtures from these additions can be more complex in that addition to the terminal carbons of the allenic system no longer gives the same product.

In the addition of ethanethiol to ~~allene~~ 1,2-butadiene, v.p.c. analysis indicated that 45.5% of the product was 1-ethylthio-2-butene (XXIV) which resulted from addition of a thiyl radical to C-1, 29.2% was 2-ethylthio-2-butene (XXV) resulting from addition to C-2, 6.3% 3-ethylthio-1-butene (XXVI) resulting from addition at C-3, and 19% was 2,3-diethylthiobutane (XXVII).

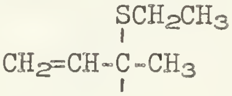
$RS-CH_2-CH=CH-CH_3$

XXIV, R = CH_3CH_2



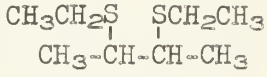
$H_3C-\overset{CH_3CH_2S}{C}=C-CH_3$

XXV



$CH_2=CH-\underset{H}{\overset{SCH_2CH_3}{C}}-CH_3$

XXVI



$CH_3-\overset{CH_3CH_2S}{CH}-\overset{SCH_2CH_3}{CH}-CH_3$

XXVII

Analysis of the unreacted olefin from the reactions indicated that no rearrangement of the 1,2-butadiene took place. Independent additions to 1-butyne, 2-butyne and 1,3-butadiene indicated that thiols add to these at the same rate as to 1,2-butadiene.

The authors concluded that the amount of initial attack on C-2 would be represented by the amount of XXV and XXVII present. Formation of XXVII from XX~~IV~~VI was ruled out by consideration of the orientation of thiyl radical additions to olefins as discussed earlier. It was shown in separate experiments that XXIV undergoes allylic rearrangement to XXVI but not enough to account for all the XXVI found in the reaction. It was also found that XXVI can rearrange to XXIV but no indication was given as to the extent of the rearrangement. Thus the actual amount of attack at C-3 is in doubt. It was also pointed out that the v.p.c. analysis did not completely exclude the diadducts 1,3-diethylthiobutane (XXVIII) and 1,2-diethylthiobutane (XXIX) or the monoadduct 2-ethylthio-1-butene (XXX).

The additions of ethanethiol and benzenethiol to 3-methyl-1,2-butadiene gave only 3-methyl-2-ethylthio- or 3-methyl-2-phenylthio-2-butene. Elemental analysis and a molecular weight determination indicated that the products were monoadducts. They were identified by acid hydrolysis to methyl isopropyl ketone and infrared spectra which indicated the absence of absorption attributable to terminal methylenes, a weak absorption attributed to a symmetrically substituted ethylene and the large difference in their spectra to those of authentic samples of the other possible monoadducts.

The amounts of center attack on various allenes by thiyl radicals are given in Table III. The amount of attack was derived from the amount of product isolated that corresponded to monoaddition to the center carbon and the amount of 1,2-diadduct. However, it is not completely clear how closely the products reflect the actual point of attack.

There is a possibility of 1,2-shifts of the RS group which would increase the amount of product corresponding to center addition if initial attack was at the terminal carbon. A shift in this direction would be expected to be favored over a shift from C-2 to C-1 since once the intermediate radical is formed, rotation can take place so that a true allylic radical would result from a C-1 to C-2 shift while a C-2 to C-1 shift would give a vinyl radical. The possibility of a 1,2-shift has been tested by van der Ploeg (22) who refluxed allylphenyl sulfide in benzene solution with AIBN initiator both with and without added benzenethiol. Only allyl phenyl sulfide was recovered, thus apparently ruling out 1,2- and allylic shifts in this case. There is a possibility that although the initial product is stable that the intermediate radical formed by attack on an allene would be more susceptible to rearrangement.

Table III
Amounts of Attack at C-2 in Radical Additions of Thiols to Allenes

Allene	Thiol	Temp. (°C)	Percent attack at C-2	Allene: Thiol Ratio	Reference
Allene	H_2S	-75	0	1:13	19
"	"	"	2	1:10	19
"	"	"	0	1:1	19
"	CH_3SH	17	12	3:1	8
"	"	-45	8	3:1	8
"	"	-75	6	3:1	8
"	CH_3CH_2SH	67	13	1.25:1	9
"	$CH_3CH_2CH_2SH$	82	30[a]	1.75:1	22
"	ϕSH	82	14[a]	1:1	22
"	ϕSH	82	27[a]	12:1	22
"	ϕCH_2SH	82	24[a]	1.2:1	22
"	"	82	none detected[a]	12:1	22
"	ϕSH	17	19	3:1	8
"	ϕSH	67	none detected	-	9
"	CH_3COSH	17	9	3:1	8
1,2-butadiene	CH_3CH_2SH	67	48.2	-	9
3-methyl-1,2-butadiene	CH_3CH_2SH	67	100	-	9
3-methyl-1,2-butadiene	ϕSH	67	100	-	9

[a] These additions were run in solution

It is also known that thiyl radical additions to olefins are reversible as shown by the isomerization of cis- and trans-2-butene (27). Thus, if attack occurred at both the terminal and center positions of allene, but the reverse step is much faster for one, the products would be derived largely from the intermediate with the slower reverse step.

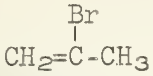
The influence of intermediate radical stability on orientation is still questionable. Little is known about the stability of vinyl radicals compared to allylic radicals. It is generally thought that the allylic radical would be more stable as are allylic intermediates in other reactions. The results on additions to the substituted allenes indicate that radical stability may be important since the amount of apparent attack at C-2 increased with increased substitution. This is consistent with the fact that secondary radicals are more stable than primary and tertiary more stable than secondary.

The effect of the polarity of the attacking radical on orientation also is not clear. Thiyl radicals are considered to be electrophilic but not as strongly as CF_3 radicals which gave terminal attack exclusively. It was expected that thiyl radicals would give both center and terminal attack. While van der Ploeg has found significant amounts of apparent center attack in reactions run in solution, other workers have found only relatively small amounts of center attack in additions run without a solvent, unless substituted allenes were used. The addition of para-substituted benzenethiols may provide information on the role of radical polarity.

The thiyl additions to allene are essentially in agreement with the radical localization calculations which indicated that terminal attack should predominate. It is not possible to tell whether attack at C-3 in 3-methyl-1,2-butadiene predominates or not, due to allylic rearrangements. It also is possible that the methyl groups on C-3 effectively block attack at that site.

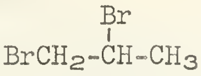
Additions of HBr - The addition of HBr to allene has been reported by Kovachic and Leitch (23) and Griesbaum and co-workers (24). When the additions were carried out in the gas phase, the products detected were 2-bromopropene (XXXI) and 1,2-dibromopropane (XXXII) which were concluded to result from initial attack of the Br radical on the center carbon of allene. These products are the same as for electrophilic additions (26). When the additions were carried out in liquid phase, significant amounts of 3-bromopropene (XXXIII) and 1,3-dibromopropane (XXXIV) were also detected and concluded

to reflect the amount of terminal attack. It was found that the amount of terminal attack increased as the temperature was lowered.



$CH_2{=}C(Br){-}CH_3$

XXXI



$BrCH_2{-}CH(Br){-}CH_3$

XXXII

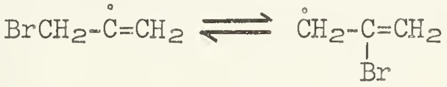
$CH_2{=}CH{-}CH_2Br$

XXXIII

$BrCH_2CH_2CH_2Br$

XXXIV

There is some question whether the amounts of XXXIII and XXXIV accurately reflect the amount of terminal attack. Skell and co-workers (25) have reported that α-bromoalkyl radicals rearrange easily. Thus in allene, the following could take place:



$$BrCH_2{-}\dot{C}{=}CH_2 \rightleftharpoons \dot{C}H_2{-}C(Br){=}CH_2$$

Such a rearrangement, resulting in increased amounts of "center attack product", would be supported by the low temperature additions if it is assumed that the rate of rearrangement is lowered more than that of hydrogen abstraction.

Summary - It has been found that CF_3 radicals add to the terminal carbons of allene exclusively while CH_3 radicals appear to attack the center carbon. The addition of thiyl radicals results in mainly terminal addition for unsubstituted allene. The amount of center addition increases in solution and when additions are to substituted allenes. The radical addition of HBr to allene resulted in mostly center addition but with increasing amounts of terminal addition at low temperatures.

It appears that the stability of the intermediate radical, the polarity of the adding radical and steric factors may affect the orientation in the radical additions to allenes. The relative importance of each is not clear.

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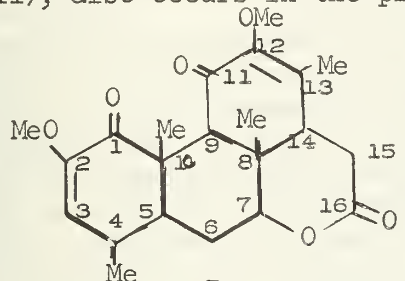
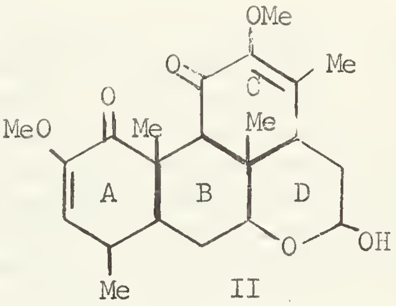
THE STRUCTURE AND BIOSYNTHESIS OF QUASSIN

Reported by Richard A. Larson November 2, 1964

Introduction: Quassin, first reported by Winckler[1], is a diterpenoid bitter substance which occurs to the extent of approximately 0.1% in the bark of Quassia amara, a subtropical flowering shrub. It has found occasional use as an insecticide. Recent investigations show that quassin has structure I. A closely related substance, neoquassin (II), also occurs in the plant.



I



II

Early Structural Studies: Wiggers[2] and Christensen[3] reported C and H analyses for quassin which differed widely from one another: Christensen assigned the empirical formula $C_{31}H_{42}O_9$. This formulation was disputed by Oliveri and Denaro[4], who preferred $C_{16}H_{22}O_5$ or $C_{32}H_{42}O_{10}$. Oliveri[5] believed that quassin possessed an anthraquinone skeleton and contained four hydroxyl groups, two carbomethoxy groups, and two carbonyl groups. The investigations of Massute[6] made the issue still more confusing, as he claimed to have separated quassin into fractions which differed by $-CH_2-$ units.

Clark[7], in 1937, was the first to make any real progress toward an understanding of the structure of quassin. By means of numerous fractional crystallizations, he was able to separate a Quassia extract into two major constituents, one of which had a melting point of 205-206° and an $[\alpha]^{20}_{D}$ of +39.8° (Chf): the other melted at 225-226° and had a specific rotation of +46.6°. He retained the name quassin for the lower-melting substance, which was present in approximately 2:1 excess. To the other substance he gave the name neoquassin. Elemental analyses suggested that the two compounds were isomers having the composition $C_{22}H_{30}O_6$. In addition, quassin could be converted to another supposed isomer, isoquassin, by treatment with CrO_3[8].

The most striking difference between the two naturally occurring products was demonstrated by their behavior in boiling 5% ethanolic KOH: quassin was extensively destroyed, whereas neoquassin could be recovered unchanged. Neoquassin, but not quassin, gave a pair of isomeric ethers when treated with EtOH or MeOH and HCl[9]. This suggested that a tertiary hydroxyl was present in neoquassin and absent from quassin.

Treatment of either compound with 3.5% HCl gave a product which analyzed for the loss of a methyl group. In addition, quassin, but not neoquassin, yielded a crystalline product which had lost two methyl groups. Thus it was likely that quassin, at least, had two methoxyl substituents.

Winnick[10] performed a zinc dust distillation upon quassin and also ran oxidative studies with $KMnO_4$ and CrO_3, but could isolate no identifiable products. Oxalic acid was the only product isolable from a HNO_3 oxidation. Its silver salt was identified by its low carbon content and by the fact that it exploded when heated rapidly!

Adams and Whaley[11] purified crude quassin on an alumina column. Two pure substances were obtained, one corresponding to Clark's neoquassin (m.p. 229-231°). The other, however, melting at 222-225°, corresponded to Clark's isoquassin. The crude mixture could be converted to isoquassin by treatment with CrO_3.

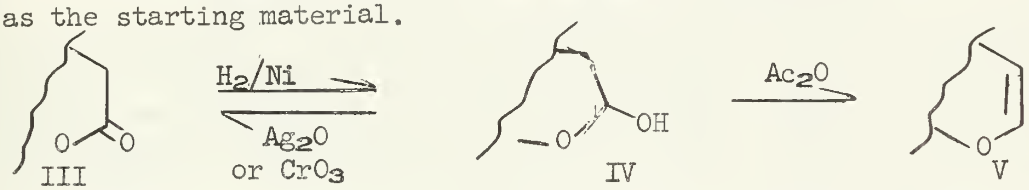
It was shown that a specimen of the substance which Clark had called quassin displayed the same IR spectrum as a cocrystallized mixture of isoquassin and neoquassin. In addition, there were extensive similarities in the X-ray diffraction patterns of the mixture and of Clark's quassin, and the optical rotation of the Clark quassin (+ 40°) was intermediate between that of neoquassin (+46°) and isoquassin (+33°).

An English group under the leadership of Robertson independently reached the same conclusions, but retained the name quassin for the substance Clark had called isoquas-

sin[12]. Robertson's terminology has been retained in the literature and in the remainder of this abstract.

Adams and Whaley disproved the earlier assumption that quassin and neoquassin were isomers: it was shown that quassin had two fewer hydrogen atoms and was represented by $C_{22}H_{28}O_6$. Infrared analysis indicated that quassin was a ketone and neoquassin the corresponding alcohol. Also implicated by the IR spectrum of quassin, Adams and Whaley thought, were a cyclopentanone ring, a conjugated ketone, and a conjugated lactone system.

London, Robertson, and Worthington[12] found more evidence for a lactone ring in quassin, first by showing that neoquassin could be purified by dissolving a crude quassin mixture in cold methanolic KOH and diluting with water. The nonlactonic neoquassin precipitated. A positive Legal test[13] suggested that the lactone was conjugated: however, the authors later disclaimed this[9] citing additional chemical evidence to show that the lactone was not α,β-unsaturated. It was observed that quassin and neoquassin could be interconverted oxidatively and reductively ($III \rightleftharpoons IV$), but the two compounds had nearly identical UV spectra. Additionally, neoquassin could be dehydrated with acetic anhydride to an α,β-unsaturated ether, anhydroneoquassin (V), which had the same UV spectrum as the starting material.

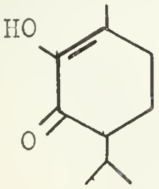


The Chromophoric Groups: Five of the six oxygen atoms in quassin had been accounted for, two as part of $-OCH_3$ groups, two in the lactone linkage, and one as a ketone from the infrared data. No -OH absorptions were visible in the IR. Evidence was presented which suggested that the last oxygen was part of an α,β-unsaturated ketone system, and that the other carbonyl oxygen was part of another such system.

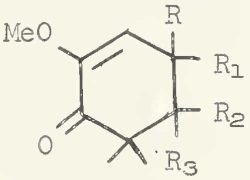
Dihydroquassin, a reduction product (Zn/HOAc or H_2/Pt) of quassin, has the same UV maximum (253 mμ) as quassin, but its intensity is reduced by 1/3. Subtracting the curve of dihydroquassin from that of quassin gives a curve having a λmax of 264 mμ (ε 4 00). Similarly, the curve derived from dihydroneoquassin, the reduction product of neoquassin, also had a λmax of 264 mμ (ε 5000), in excellent agreement.

The monodemethylation products norquassin and norneoquassin had ultraviolet spectra similar to those of the parent substances in acid solution, but in base a new peak appeared at 314 mμ (ε 4000), and the main peak was reduced in intensity. This behavior was shown by comparison with published spectra[14,15,16] to be characteristic of the enols of α-diketones. Further evidence for this structural unit was provided by the strong color reactions of the demethylated products with ferric salts, and by their IR spectra which showed a sharp absorption at 3390 cm^{-1} comparable to one at 3410 cm^{-1} in the spectrum of diosphenol (VI)[17]. In addition, the broad "conjugate chelation" band at 2900-3500 cm^{-1}, characteristic of β-diketones, was absent[18].

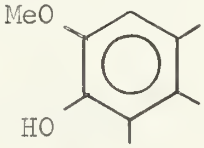
The partial structure VII was suggested for the chromophoric system giving rise to the above observations. It was called chromophore A, and its structure was partly based on a selenium dehydrogenation experiment which gave the phenol VIII in small yield from neoquassin[19].



VI



VII

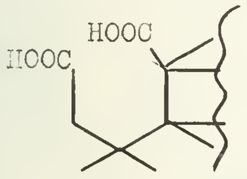


VIII

The Robertson group gives no real justification for the gem-dimethyl shown in VII. It may be based on a doublet in the IR at 1350 and 1380 cm^{-1}.

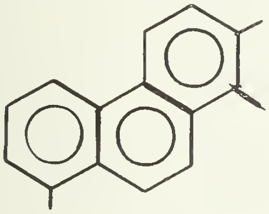
The other chromophore, designated B, with its UV absorption of 253 mμ, was assigned to an α,β,β-trisubstituted-α,β-unsaturated ketone system on the basis of Woodward's rules[20], which predict a maximum of 249 mμ.

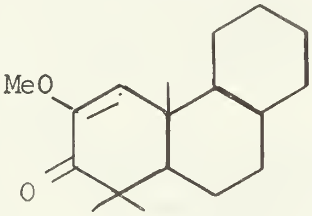
Further Structural Studies: When anhydroneoquassin (partial formula V) was hydrogenated, a compound called deoxoquassin was obtained. Treatment with acid converted this material to an enol, deoxonorquassin[21]. Oxidation with alkaline H_2O_2 gave a nonenolic dibasic acid, which yielded a monomethyl ester when reacted with methanolic HCl and a diester on treatment with diazomethane. Hydrolysis of the diester gave a different monoester. Thus it was assumed that one of the carboxyl groups was tertiary, and the diacid was assigned the partial structure IX.

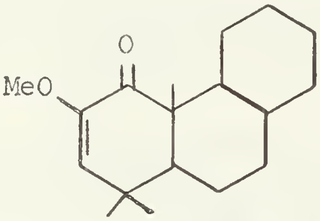

IX

The UV spectrum of IX was that of chromophore B. When reduced with $LiAlH_4$, a noncrystalline product with no UV absorption above 220 mμ was produced, strengthening the hypothesis that chromophore B was an α,β-unsaturated ketone.

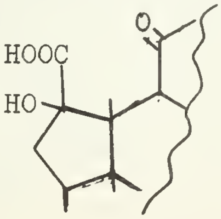
A Clemmensen-Martin reduction of neoquassin gave a noncrystalline substance having no UV absorptions[22]. When this substance was dehydrogenated with selenium, a crystalline hydrocarbon $C_{17}H_{16}$ was obtained. Its structure was assigned as 1,2,8-trimethylphenanthrene (X) on the basis of comparisons with an authentic sample. Two possible partial structures, XI and XII, were proposed by inserting chromophore A into a perhydrophenanthrene skeleton. The locations of the lactone system, the other -OMe group, and chromophore B were not assigned. The investigation of the structure of quassin was next taken up by a Canadian group under the leadership of Valenta [23,24]. The NMR spectrum of the compound showed four C-methyl groups; a doublet at τ 8.86 (J = 7 cps) and singlets at τ8.15, 8.45, and 8.79. Deuteration of neoquassin in refluxing CH_3OD in the presence of $NaOCH_3$ led to the incorporation of 5.5 deuterium atoms and the disappearance of the τ 8.15 signal. The doublet at τ 8.86 became a singlet. These observations are taken to mean that the protons in question are either α or vinylogously α to a carbonyl group. In addition a vinylic proton was observed as a doublet at τ 4.77 (J = 2 cps) which disappeared after quassin was hydrogenated.

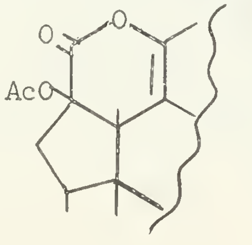

X

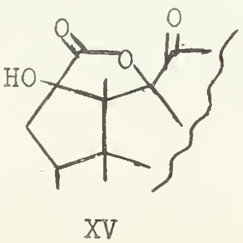

XI


XII

The benzilic acid rearrangement product of quassin, norquassinic acid, which had first been obtained by Beer, Hanson, and Robertson[21], was assigned partial structure XIII on the basis of the following reasoning. First, the dihydro products of ring A of quassin, which contains chromophore A, show no carbonyl absorptions above 1715 cm^{-1}; thus ring A is a six-membered ring. Secondly, the benzilic acid rearrangement product of deoxonorquassin, when treated with H_2SO_4, lost the elements of HCOOH and gave a ketone with IR absorption at 1740 cm^{-1}; thus a five-membered ring had been produced. Thirdly, XIII when heated with acetic anhydride - sodium acetate gave a lactone, which on the basis of IR evidence appeared to be the acetate of a six-membered enol lactone

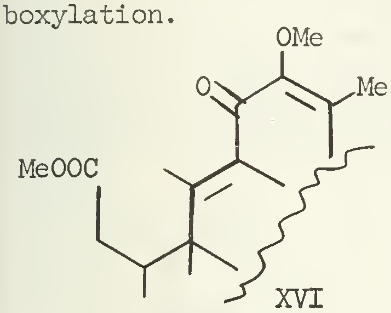

XII


XIV

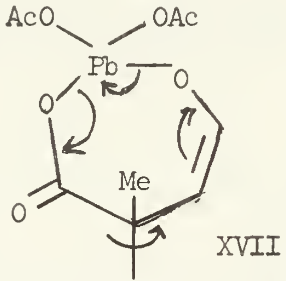

XV

(XIV). Finally, another lactone could be prepared by treating XIII with lead tetraacetate. It was assigned structure XV, since it had an IR band at 1785 cm^{-1} (γ-lactone) and its NMR spectrum showed that no protons had been unshielded by the new lactone ring, and thus closure would have had to take place at a tertiary carbon atom.

When the monomethyl ester obtained by treating dibasic acid IX with methanolic HCl is heated with lead tetraacetate, an unusual oxidative decarboxylation occurs. The product, a doubly unsaturated ketone, was assigned structure XVI. A seven-membered cyclic transition state, XVII, was proposed as the mechanism of the decarboxylation.



XVI

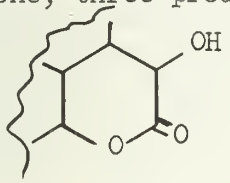


XVII

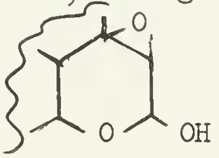
The NMR spectrum of XVI showed two methyl groups attached to double bonds (τ 7.95, 8.16), one secondary (τ 9.21, doublet), and one tertiary (τ 8.94) C-methyl. Since one of these methyls is on the newly formed double bond, the results establish that quassin cannot contain a gem-dimethyl grouping.

Additional points of the structure which can also be assigned include the O-methyl adjacent to the carbonyl carbon in XVI, placed there since the acid hydrolysis product of norquassinic acid (XIII) shows the properties of a diosphenol, and the methyl group which had been completely deuterated, since it is attached to the double bond and is vinylogously α to the carbonyl.

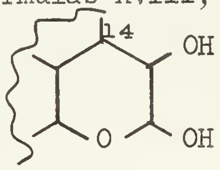
The position of the lactone ring of quassin relative to chromophore B was determined by oxidative studies. When anhydroneoquassin was oxidized with $KMnO_4$ in cold acetone, three products were obtained, having the partial formulas XVIII, XIX, and XX.



XVIII



XIX

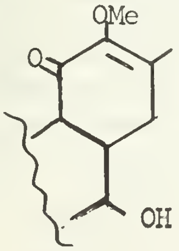


XX

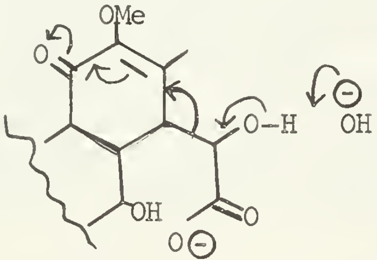
When XX was treated with HIO_4, an intermediate aldehyde-formate arose, which had NMR signals at τ 0.31 (aldehyde, doublet), and τ 2.17 (formate, singlet). These results show the presence of one proton at C_{14}. Basic hydrolysis of the formate and oxidation of the product with CrO_3 gave a γ-lactone (IR 1775 cm^{-1}), showing that quassin must be a δ-lactone.

Hydroxylactone XVIII, when refluxed with aqueous base, lost a two-carbon fragment. The product was the secondary alcohol XXI. This defines the position of the lactone ring, since XXI must have arisen from an elimination of the type shown in XXII.

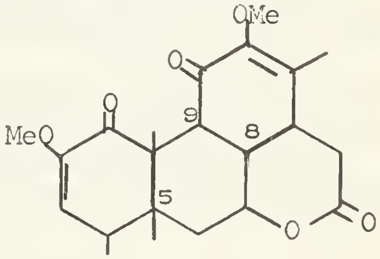
The Valenta group now could propose XXIII as the structure of quassin.



XXI



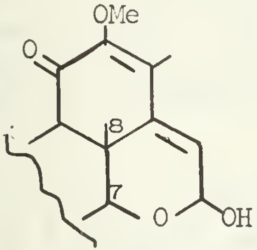
XXII



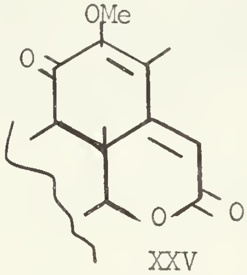
XXIII

This structure was soon attacked with respect to the position of the methyl group at C$_5$. Carman and Ward pointed out[25] that a one-proton singlet, assignable to the C$_9$ methine hydrogen, appears in the spectra of all quassin derivatives. This proton, being unsplit, would require a coupling constant of zero between it and the C$_8$ proton, and thus a rather special conformational requirement; a dihedral angle of ~90° between the two protons throughout the whole series of derivatives[26]. A more probable alternative formulation would be that a methyl group, rather than a proton, be located at C$_8$.

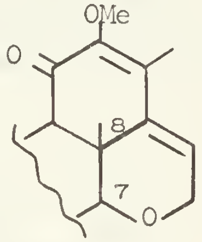
This suggestion was strongly supported by additional evidence forthcoming on several fronts. First, a dehydrogenation product obtained by treating neoquassin with acetic anhydride- sodium acetate was shown to be the dienone XXIV[24]. It could be oxidized with Ag$_2$O to the conjugated lactone XXV. Neither compound could be aromatized with acid or base, or by unspecified "mild dehydrogenation conditions". Carman and Ward likewise failed to aromatize anhydroneoquassin with refluxing 4% KOH in ethanol[27];, obtaining instead the related dienone XXVI.



XXIV

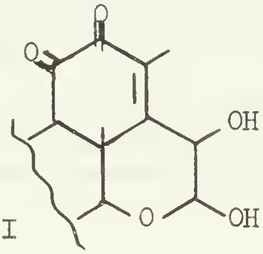


XXV

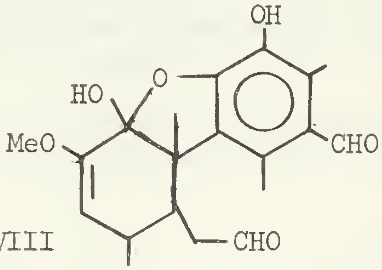


XXVI

Still more conclusive proof was presented when the C ring actually was aromaitzed under drastic conditions involving cleavage of the C$_7$ - C$_8$ bond[24]. Epoxide XIX, one of the oxidation products of anhydroneoquassin, was hydrolyzed with HCOOH, giving the diketone XXVII. This product, when refluxed with methanolic KOH, underwent oxidative fission and a product was isolated which was formulated as XXVIII. The same product was formed when XXVII was treated first with HIO$_4$ and then with base. A vinylic hydrogen was still present (τ 5.19, doublet) but the absence of UV absorption characteristic of chromophore A was taken to indicate the presence of a hemiacetal function. The substance had NMR signals corresponding to two aldehyde groups. One of these was aromatic as shown by an IR band at 1675 cm^{-1}. In addition, there were NMR signals for two aromatic methyl groups (τ 7.46, 7.53), conclusively defining the position of the 8-methyl group and confirming the structure of quassin as I.



XXVII

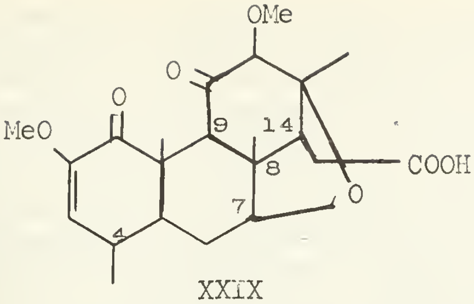


XXVIII

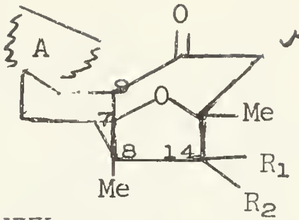
Stereochemistry: A stereochemical investigation of quassin is complicated by the existence of three epimerizable positions - carbons 4, 9, and 14. Valenta, et al., in their investigation, attempted to prove that the epimerizations they observed occurred at identifiable positions and tried to relate these epimerizations to the changes in properties and stability of the compounds isolated[28].

When quassin was refluxed with aqueous base, an acidic product, pseudoquassinolic acid, was formed. It no longer showed olefinic C-CH$_3$ in its NMR spectrum, and had the UV absorption characteristic of chromophore A. The IR spectrum of its methyl ester showed no -OH bands. On the basis of this evidence the product was assigned structure XXIX. (However, C and O analyses were somewhat outside accepted limits, and -OCH$_3$ and -CCH$_3$ analyses were very poor.)

Model studies showed that the formation of the new five-membered ether ring imposes stringent requirements of the configuration of pseudoquassinolic acid: it must have the stereochemistry indicated in XXX. An epimerization presumably took place



XXIX

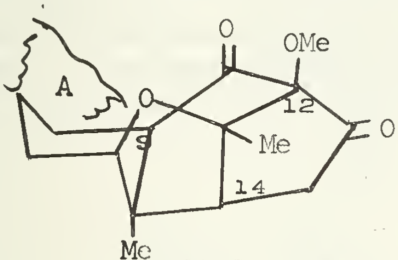


XXX

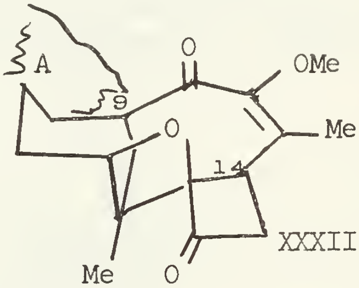
R_1 AND R_2 =
-H and
$-CH_2COOH$
(not yet defined)

(quassin can be recovered unchanged from cold base).

When pseudoquassinolic acid was boiled with acetic anhydride-sodium acetate, a dehydration product, pseudoquassin, was formed. It has the same empirical formula as quassin, but contains no ring C chromophore and includes a new cyclopentanone ring (1770 cm^{-1} in IR). It was concluded that an intramolecular acylation occurred at C_{12}, giving XXXI. There is also a possibility that acylation could have taken place at C_9, but this has the same stereochemical significance.



XXXI

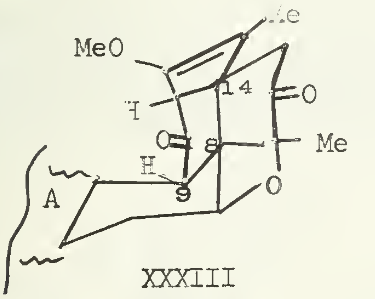


XXXII

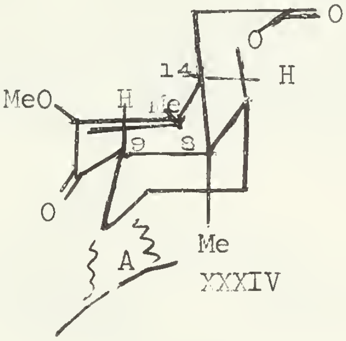
Under more drastic conditions (pyrolysis), pseudoquassinolic acid was converted into alloquassin, an isomer of quassin. This compound contained both chromophores, and unlike quassin was unstable in cold aqueous base, reverting to pseudoquassinolic acid. This observed instability suggests structure XXXII, in which ring C is slightly distorted and the lactone ring is ~~in~~ the boat form.

Rationalization of the above results is as follows: pseudoquassin is formed under mild conditions, and requires merely an acylation. The formation of alloquassin requires a β-elimination of the ether function, followed by an epimerization C_{14} and ring closure. Thus formula XXIX (R_1= $-CH_2COOH$, R_2= -H) can be assigned to pseudoquassinolic acid.

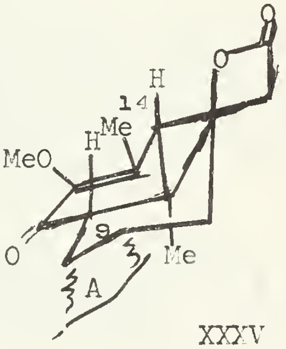
Alloquassin has thus been assigned one of the four possible stereostructures (ignoring ring A and position 4 for the moment). Three remaining structures, XXXIII, XXXIV, and XXXV, remain under consideration.



XXXIII



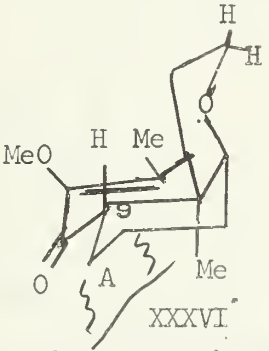
XXXIV



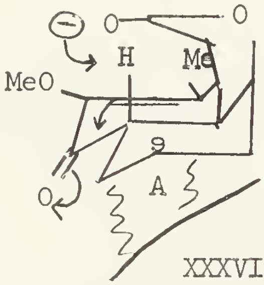
XXXV

When quassin was heated with acetic acid or with cold methanolic HCl it equilibrated with another isomer, termed isoquassin by Valenta, et al. (although not, of course, identical with the isoquassin of Clark). These isomers appeared to be present in approximately equal quantities and thus are probably similar in stability. Alloquassin was shown to be absent in a TLC study. Examination of Dreiding models of XXXIII-XXXV shows that the strain free structure XXXIII should be significantly more stable than the other two in terms of 1,3-interactions and should probably be eliminated from consideration as a representation of quassin or isoquassin. While it might be expected that structure XXXV, which incorporates a highly strained twist form lactone ring, should be less stable than XXXIV, model studies show that certain 1,3-distances, notably that between the C_8 methyl and axial substituents at C_{10}, are reduced. In addition, the lactone ring helps to eliminate otherwise objectionable 1,2-interactions.

Quassin and neoquassin show very similar ORD curves, and can be interconverted fairly easily. This argues for a close configurational similarity between the two, and suggests that quassin may be describable by formula XXXIV, since the introduction of another tetrahedral carbon atom into ring D would perhaps tip the balance in favor of the chair form. This hypothesis is supported by deuteration experiments, which show that the C_9 proton of neoquassin is completely exchanged after four hours of reflux with $CH_3OD/NaOCH_3$. In contrast, the corresponding proton of deoxoquassin, whose stereoformula will be postulated as XXXVI, shows no measurable exchange under the same conditions. A reasonable explanation for this phenomenon proposes an intramolecular catalysis in the case of neoquassin involving intermediate XXXVII.



XXXVI

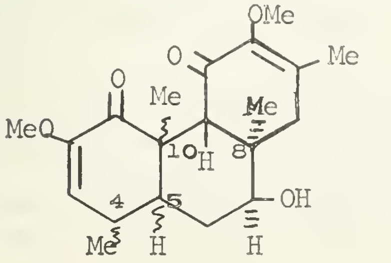


XXXVII

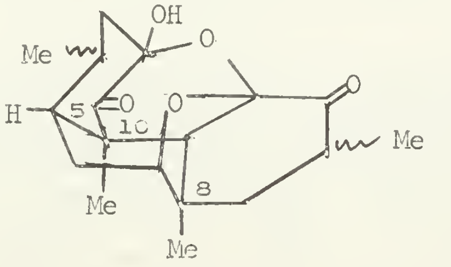
To complete the stereochemical assignments, the configurations at C_4, C_5, and C_{10} must be determined.

The NMR signal of the C_3 proton is a doublet in quassin and its derivatives. J_{34} is numerically very small, averaging 2.1 cps[27,28]. This should correspond to a dihedral angle calculated from the Williamson-Johnson equation[26] of either 63° or 111°. From models, the angle between the C_3 hydrogen and an equatorial C_4 proton is approximately 20°; if the C_4 hydrogen is axial the angle is 110°. The hydrogen in question was thus assigned an axial position. However, the possible dangers in using coupling constants to determine stereochemistry, particularly in systems with π-electrons, have been pointed out[29,30,31].

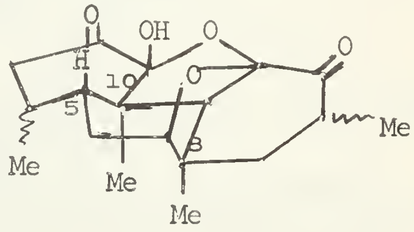
When the alcohol XXI, which can be given the more complete formula shown, is treated with acid, a neutral product is obtained which has lost both O-methyl carbons and has neither UV absorption nor α-diketone units. Since the two diosphenolic chromophores have disappeared, an internally bridged compound must have arisen. Only two formulas, XXXVIII and XXXIX, are compatible with this bridged structure.



XXI

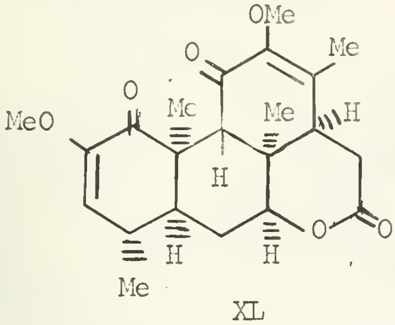


XXXVIII

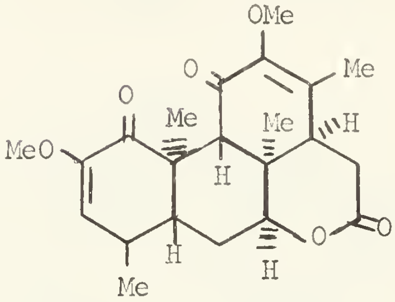


XXXIX

While no clear decision can be made between these two structures, it is evident that the two methyl groups at C_8 and C_{10} must be on the same side of the perhydrophenanthrene skeleton for the bridging to take place. Thus there are two possible structures for quassin, epimeric at C_5, XL and XLI.



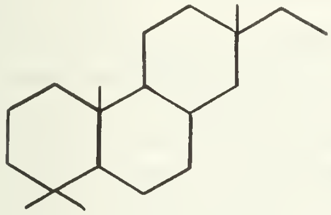
XL



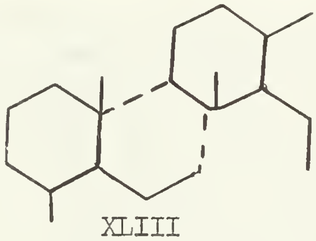
XLI

Biosynthesis: The first biogenetic hypothesis published for quassin was that of Valenta, et al., who speculated that it could arise from a pimarane (XLII) skeleton by a series of 1,2-shifts[23]. At this time structure XXIII had been postulated, and this would only require two such shifts: structure I would require five.

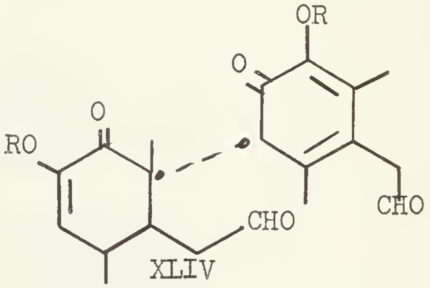
A possibly more reasonable proposal was suggested by Thomas[32], involving the oxidative coupling of two identical monterpene units (XLIII). Valenta, Papadoupolos, and Podesva quote this scheme[24], but in this article the coupling units are represented as **fully** substituted phenolic intermediates (XLIV).



XLII

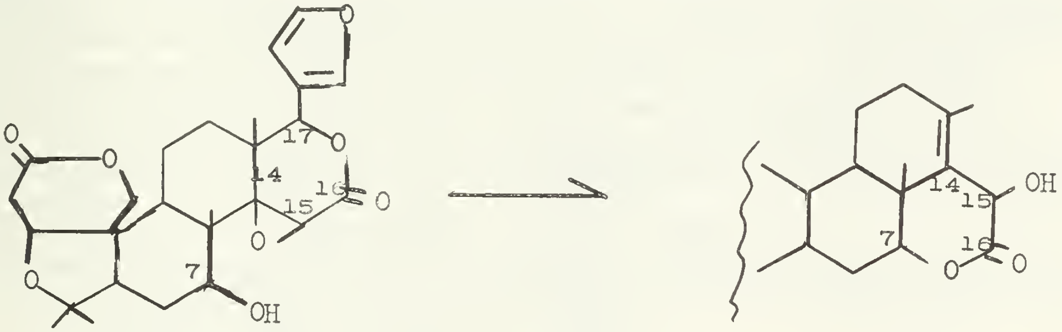


XLIII



XLIV

More recently another intriguing hypothesis has been proposed by Bredenburg[33] and independently by Dreyer[34] based on the limonol-merolimonol rearrangement. Limonol (XLV), when treated with base, undergoes an extensive rearrangement, yielding merolimonol (XLVI), which has essentially the same carbon skeleton as quassin[35]. Two mechanisms have been proposed[36,37]. A similar reaction takes place with a variety of related C_{26} compounds[34] which occur in plant families closely related to the Simaroubaceae, from which quassin is isolated.



XLV

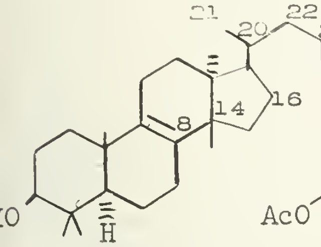
XLVI

The stereochemistry of merolimonol and the related compounds, based on their NMR splitting patterns[34] is consistent with that proposed for quassin.

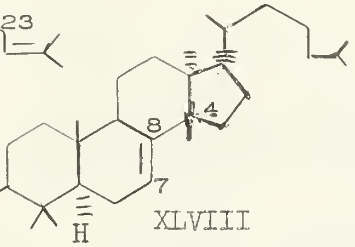
Published speculations[35] on the biosynthesis of limonin, precursor of limonol, lend further believability to the newly proposed scheme. Limonin is supposed to arise from a triterpenoid of the euphol (XLVII) type. Carbons 20-23 form the furan ring, ring D is oxidized to a 16-ketone and is expanded in a Baeyer-Villiger-like reaction, and a methyl group migrates from C_{14} to C_8. In connection with the last-mentioned step, it is noteworthy that a close laboratory analogy exists: dihydrobutyrospermol acetate

(XLVIII) can be oxidized to a 7-ketone in which the required migration has taken place[38].

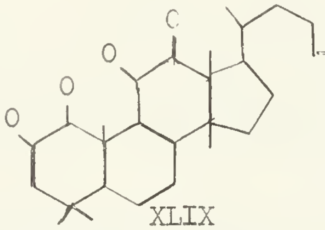
The supposed precursor of quassin, along these lines, may be a triterpene such as XLIX. Loss of one of the C_4-gem-dimethyls might occur by oxidative decarboxylation. It is notable that a near relative of quassin, nimbin, (L) appears to represent an intermediate oxidation state[39].



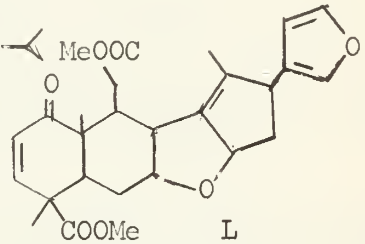
XLVII



XLVIII



XLIX



L

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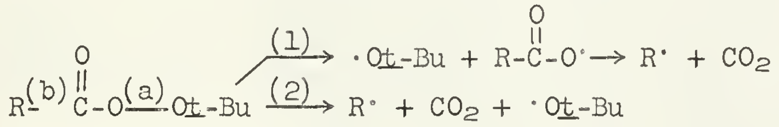
THE DECOMPOSITION OF PERESTER COMPOUNDS

Reported by Thomas Sharpe   November 9, 1964

Introduction - This seminar will deal mainly with the mechanisms of the homolytic decompositions of a series of peroxalates and percarbonates and an unrelated group of perester compounds, the majority of which can undergo either homolytic or heterolytic decomposition depending on the nature of the solvent. The work of Bartlett and coworkers on the decomposition of the t-butyl peracetates has been reviewed.[1,2] Therefore, only a brief account of their findings will be presented here. No effort will be made to cover work dealing with those peresters which on decomposition could afford nonclassical, free radical intermediates[3,4,5] or the related area of anchimeric assistance in perester decompositions,[6,7,8] since most of the work in these areas has also been reviewed.[9]

The Peracetates - The results of Bartlett and coworkers show that there exist two possible modes for the spontaneous thermal decomposition of t-butyl peresters of type I.[10,11] In mechanism (1) the primary act of decomposition involves the rupture of the peroxidic bond (a) to produce t-butoxy radical and a carboxylate radical, the latter of which usually rapidly decomposes to give alkyl radical and a molecule of CO_2. In the alternate mechanism (2), bonds (a) and (b) cleave simultaneously in the transition state, and alkyl radical, t-butoxy radical and carbon dioxide are produced in a single rate-determining step. It was shown that those peresters which can produce a radical


I

$$R\overset{(b)}{-}\overset{O}{\overset{\|}{C}}-O\overset{(a)}{-}Ot\text{-}Bu \begin{cases} \xrightarrow{(1)} \cdot Ot\text{-}Bu + R-\overset{O}{\overset{\|}{C}}-O\cdot \longrightarrow R\cdot + CO_2 \\ \xrightarrow{(2)} R\cdot + CO_2 + \cdot Ot\text{-}Bu \end{cases}$$

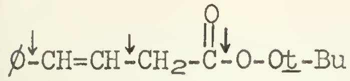
(R·) appreciably more stable than the methyl or phenyl radical decompose by mechanism (2), the concerted two bond cleavage mechanism. A potentially useful experiment to distinguish between these two possible mechanisms would be to carry out the decomposition in the presence of a hydrogen donating solvent such as cumene. If mechanism (1) were operative, the intermediate carboxylate radical could abstract hydrogen from the solvent producing a carboxylic acid. The formation of carboxylic acid from mechanism (2) being impossible, the isolation or non-isolation of such as a reaction product could be used as a criterion in determining the correct mechanism. However, such considerations are not helpful. Unless the carboxylate radical possesses some special stability, it rapidly decomposes before it can abstract hydrogen from the solvent. Furthermore, when acid is formed in a perester decomposition, it generally results from an induced decomposition rather than from an intermediate carboxylate radical. The most useful criterion for distinguishing between the two possible mechanisms is a consideration of the rates of decomposition. Because of the incipient formation of a molecule of CO_2 in the transition state for the concerted decomposition, peresters decomposing by this process have considerably higher decomposition rates than those decomposing by the step-wise mechanism. Table I lists rate data obtained for a few peresters.

Table I: Decomposition Rates for Peresters RCOOOt-Bu

R	$t_{1/2}$ at 60°, min.	rel. rate	$\Delta H^{\ddagger}$ (kcal./mole)	$\Delta S^{\ddagger}$ (e.u.)
CH_3	5×10^5	1	38	17
ϕCH_2	1700	300	28.7	3.9
Cl_3C	970	520	30.1	8.9
$\phi CH{=}CHCH_2$	100	5000	23.5	-5.9
ϕ_2CH	26	2×10^4	24.3	-1.0

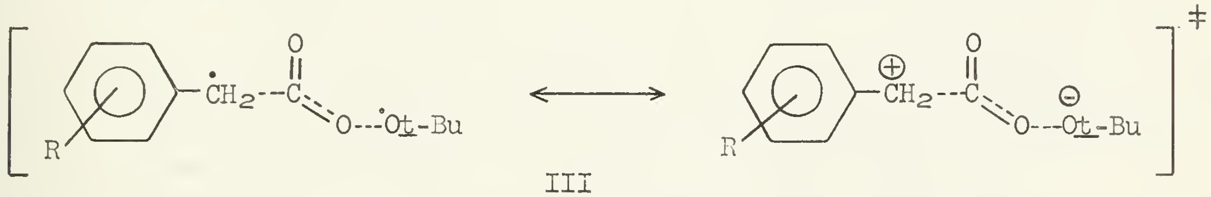
Since t-butyl peracetate decomposes by a two step mechanism, the huge difference in rate of decomposition between it and t-butyl phenylperacetate must be due to a concerted mechanism in the latter. Since in the transition state for the concerted decomposition, the radical R· is taking form in the transition state, its stability is reflected in the rate of decomposition of the perester. This is the reason for the large differences in rate for the last four peresters in Table I. However, if maximum resonance stabilization is to be achieved in the transition state, the rotations about

certain bonds (those marked with an arrow in II) must be restricted. This gives rise to a lower $\Delta S^{\ddagger}$. That some degree of charge separation exists in the transition state was shown when a series of substituted *t*-butyl phenylperacetates was investigated.[12] A good Hammett plot was obtained using σ^{+} values for the substituents. The better correlation with σ^{+} than with σ and the negative value of ρ (-1.09) led Bartlett and Rüchardt to postulate a charge separated transition state as in III.



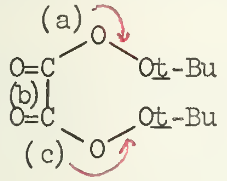
$\phi\overset{\downarrow}{-}CH=CH\overset{\downarrow}{-}CH_2-\overset{O}{\overset{\|}{C}}\overset{\downarrow}{-}O-O\textit{t}-Bu$

II



III

The Peroxyoxalates - That certain peresters decompose with the concerted cleavage of two bonds led to speculation whether certain suitably constituted peresters might decompose with the cleavage of three or more bonds in concert. The first perester studied with this possibility in mind was di-*t*-butyldiperoxyoxalate (IV).[13]



IV

This perester, with concerted cleavage of bonds (a), (b), and (c), would yield two molecules of CO_2 and two *t*-butoxy radicals. The formation of the two stable CO_2 molecules in the transition state could provide the necessary driving force for facile thermal decomposition.

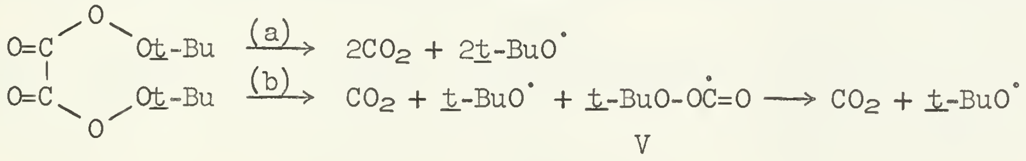
The products of the decomposition of IV are shown in Table II. The yields of CO_2 were very nearly quantitative in benzene and cumene, two moles of CO_2 being formed per mole of IV decomposed.

Table II: Products of the Decomposition of Di-*t*-butyldiperoxyoxalate at 45°

Compound	moles/mole perester	
	In Benzene	In Cumene
methane	0.14	
ethane	0.17	
carbon dioxide	1.92	2.01
acetone	0.77	0.03
t-butyl alcohol	1.03	1.77
biphenyl	0.07	
bicumyl		0.86
% *t*-butyl accounted for	90	91
% CO_2 accounted for	96	100

The kinetics of the decomposition of IV were studied in benzene at 35°, 45° and 55°. Concentrations of IV were varied over a tenfold range at each temperature, and good first-order kinetics were observed.

The activation parameters determined for IV are $\Delta H^{\ddagger} = 25.5$ kcal./mole and $\Delta S^{\ddagger} = 5.1$ e.u. For comparison with the peresters in Table I, the calculated half-life for IV at 60° is 6.8 min. This fast rate of decomposition of IV is good evidence that at least one molecule of CO_2 is being formed in the transition state.



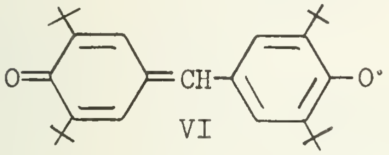
IV

The clean decomposition products are certainly consistent with a concerted

three bond mechanism (a); however, they are also consistent with the concerted two bond mechanism (b) if the carbo-t-butylperoxy radical (V) is so unstable that it decomposes before it can abstract hydrogen from the solvent or combine with other radicals present in solution.

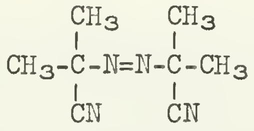
The high rate of decomposition is certainly consistent with the concerted three bond mechanism, a process where two CO_2 molecules are forming in the transition state. However, this high rate might also arise if only two bonds are cleaving in concert even though the carbo-t-butylperoxy radical (V) does not possess the stability associated with a benzyl or benzhydryl radical which furnishes the driving force for the concerted two bond cleavages in the peracetates discussed above. The carbon-carbon oxalate bond is one linking two highly polarized carbon atoms and would be expected to be relatively weak. For example, the central carbon-carbon bond dissociation energy in biacetyl is reported to be 60 kcal./mole.[14] Such ground state destabilization effects have been shown to be important in a series of substituted benzoyl peroxides.[15]

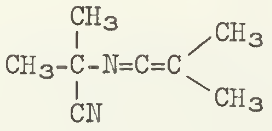
Di-t-butyldiperoxyoxalate was decomposed by Bartlett and Funahashi in the presence of the stable free radical galvinoxyl (VI).[16] These workers found the first-order rate constant for the decomposition of IV obtained by measuring the disappearance of the scavenger (VI) to be 99.5% of the value obtained by observing the disappearance of the perester carbonyl peak in the infrared. This result indicates that 99.5% of the di-t-butyldiperoxyoxalate molecules that decompose produce scavengeable radical pairs. From these results, Bartlett set an upper limit on the cage effect in the decomposition of IV at one percent.



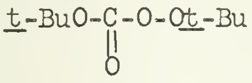
VI

If IV decomposes with the concerted cleavage of three bonds, the lack of any cage recombination of the t-butoxy radicals could be due to the two CO_2 molecules which separate the t-butoxy radicals in the solvent cage. Hammond has found that there is less cage effect in the decomposition of AIBN (VII) where there is a molecule of nitrogen between the two cyanoisopropyl radicals in the solvent cage than in N-cyanoisopropyl-dimethylketene imine (VIII), where the cyanoisopropyl radicals are formed without the nitrogen molecule.[17,18]

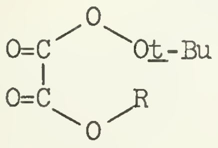

$$CH_3\text{-}\underset{CN}{\overset{CH_3}{C}}\text{-}N{=}N\text{-}\underset{CN}{\overset{CH_3}{C}}\text{-}CH_3$$
VII


$$CH_3\text{-}\underset{CN}{\overset{CH_3}{C}}\text{-}N{=}C{=}C(CH_3)_2$$
VIII

If IV decomposes with the concerted fission of two bonds, the absence of any cage effect suggests two possibilities: either the product of cage combination, di-t-butylmonoperoxycarbonate (XV), is very unstable and decomposes much faster than IV or the carbo-t-butylperoxy radical (V) is so unstable that it decomposes before it can combine with t-butoxy radical in the solvent cage. The first of these possibilities was ruled out when it was found (see below) that XV is stable at the temperatures employed for the decomposition of IV.[19] It was therefore concluded that if the carbo-t-butylperoxy radical (V) is formed at all in the decomposition of IV, it has a shorter lifetime than the acetoxy radical, to which Herk, Feld, and Szwarc have assigned a lifetime of 10^{-9} to 10^{-10} second.[20]

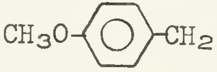

$$t\text{-BuO-}\underset{O}{\underset{\|}{C}}\text{-O-O}t\text{-Bu}$$
XV

In an effort to distinguish between the two possible mechanisms for the decomposition of IV, a series of t-butylmonoperoxyoxalates (IX) was investigated.[21]

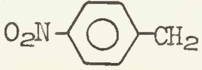


IX

IX-a: R = CH_3CH_2

IX-b: R = 

IX-c: R = ϕCH_2

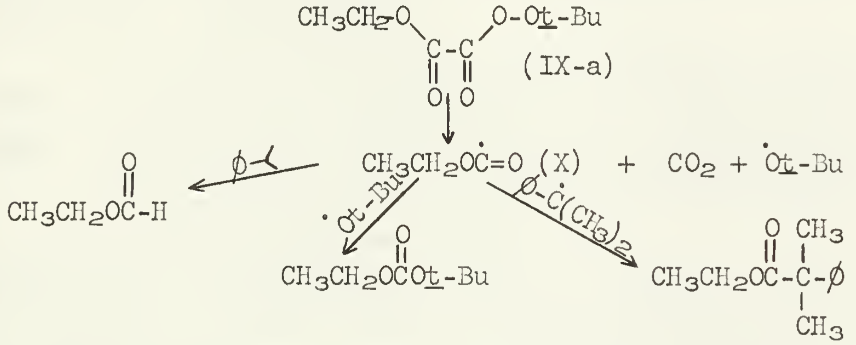
IX-d: R = 

Products from the decomposition of ethyl-t-butylmonoperoxyoxalate (IX-a) are listed in Table III. As can be seen from the table, products are found that derive from the intermediate carboethoxy radical (X). Such products conclusively rule out a mechanism involving the

concerted breaking of three bonds. At least two bonds must break in concert to account for the high rate of decomposition, the calculated half-life at 60° being 43 minutes.

Table III: Products of the Decomposition of IX-a at 45°

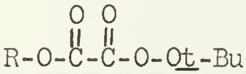
Product	moles/mole perester	
	In benzene	In cumene
carbon dioxide	1.31	1.12
t-butyl alcohol	0.54	0.75
acetone	0.18	
methane	0.03	
ethane	0.11	0.20
ethylene	0.04	
ethyl t-butyl carbonate	0.23	0.28
ethyl benzoate	0.07	
ethyl phenyldimethylacetate		0.23
ethyl formate		0.15
biphenyl	0.02	
bicumyl		0.32
t-butyl group accounted for	0.95	1.00
carbonyl group accounted for	1.62	1.78



The considerable difference in the nature of the products arising from the decomposition of ethyl t-butylmonoperoxyoxalate (IX-a) and di-t-butyldiperoxyoxalate (IV) does not, however, necessitate a three bond mechanism in the latter, since the carbo-t-butylperoxy radical (V) might decompose before it can undergo the reactions outlined above for X . It even appears reasonable that V would be more unstable than X due to the relative weakness of the oxygen-oxygen bond in the former.

The relative rate constants for the monoperoxyoxalates (IX) are shown in Table IV.

Table IV: Relative Rate Constants and Activation Parameters for R-O-C-C-O-Ot-Bu in Benzene



$R-O-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-O-O$t-Bu

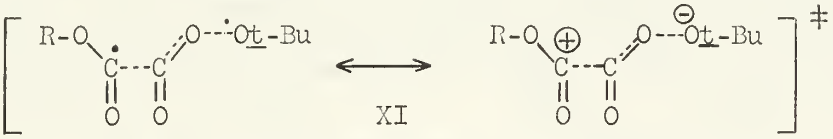
R	relative rate at 45°	$\Delta H^{\ddagger}$(kcal/mole)	$\Delta S^{\ddagger}$(e.u.)
$(CH_3)_3CO$	20.0	25.5	5.1
$CH_3OC_6H_4CH_2$	5.2	26.2	4.6
C_2H_5	3.5	26.9	6.0
$C_6H_5CH_2$	2.8	26.6	4.5
$O_2NC_6H_4CH_2$	1.0	27.9	6.8

The products of the decomposition of benzyl t-butylmonoperoxyoxalate (IX-c) in benzene were also determined and a 24% yield of benzyl t-butyl carbonate was obtained. The products from the decomposition of IX-b and IX-d were not determined.

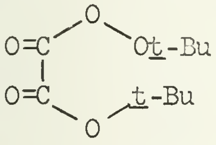
The high rate of decomposition of these monoperoxyoxalates must be due to the relative weakness of the carbon-carbon oxalate bond discussed above, since the three bond mechanism is not operative.

Although $\Delta H^{\ddagger}$ for the decomposition of IV is lower than the $\Delta H^{\ddagger}$ for any of the monoperoxyoxalates, this in itself cannot be taken as evidence for the three bond mechanism in IV. As the authors point out, the difference in $\Delta H^{\ddagger}$ between IV and IX-b is less than the difference in $\Delta H^{\ddagger}$ between IX-b and IX-d, and the latter two compounds both decompose by the two bond mechanism.

However, by using the two bond mechanism for the decomposition of IV, Bartlett and Pincock found they could not explain why it decomposed faster than the monoperoxyoxalates. The trend in the rates of decomposition (see Table IV) for the monoperoxyoxalates could be explained on the basis of a charge separated transition state (XI) similar to that proposed above for the substituted phenyl peracetates. The ethyl ester decomposed at a faster rate than the benzyl ester supposedly because the dipole moment associated with the phenyl-carbon bond in the latter was unfavorable to the development of positive charge on its side of the molecule. Now if di-*t*-butyldiperoxyoxalate decomposes by this mechanism it would be expected to decompose at a slower rate than the monoperoxyoxalate because of the unfavorable inductive effect of the *t*-butoxy group. Thus the alternate three bond mechanism for di-*t*-butyldiperoxyoxalate was suggested to explain its faster rate of decomposition.



XI



XII

The observation that the rates of decomposition in the monoperoxyoxalates increased with increasing electron releasing power of the alkyl group prompted the investigation of the rate and products of decomposition of di-*t*-butylmonoperoxyoxalate (XII).[22] The *t*-butyl group in this perester would have greater electron release than the corresponding substituents in the monoperoxyoxalates discussed above.

The products of the decomposition of XII in cumene are shown in Table V. In contrast to di-*t*-butyldiperoxyoxalate (IV), which gives only CO_2, *t*-butyl alcohol, and bicumyl in cumene, XII gives 37-44% yields of di-*t*-butyl carbonate. The most striking feature of this perester is its high rate of decomposition; at 45° it decomposes almost three times faster than di-*t*-butyldiperoxyoxalate (IV). Its relative rate for comparison with the peresters in Table IV is 57. The activation parameters for XII are: $\Delta H^{\ddagger} = 24.0$ kcal/mole and $\Delta S^{\ddagger} = 2.5$ e.u.

Table V: The Products of the Decomposition of XII in Cumene at 24.60°

Compound	moles/mole perester	
	Run 1	Run 2
CO_2 by wt.	1.54	1.57
CO_2 by volume	1.55	1.53
isobutane	0.21	0.27
isobutylene	0.03	
t-butyl alcohol	0.57	0.60
di-*t*-butyl carbonate	0.44	0.37
bicumyl	0.41	0.42

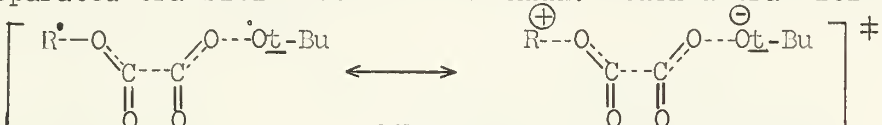
As pointed out above, if carbo-*t*-butyldiperoxy radical (V) is formed at all in the decomposition of di-*t*-butyldiperoxyoxalate (IV), it is extremely unstable and decomposes before it can combine with *t*-butoxy radical in the solvent cage. This conclusion receives support in the finding that about 80% of the di-*t*-butylcarbonate formed in the decomposition of XII is a true cage product. This was determined by decomposing XII in an equivalent amount of galvinoxyl (VI) and comparing the di-*t*-butylcarbonate yield to that obtained without the galvinoxyl. These results are shown in Table VI. As indicated by the 50% yield of CO_2 and the low yield of isobutane and isobutylene, the carbo-*t*-butoxy radical can be scavenged by the galvinoxyl before it decomposes to CO_2 and *t*-butyl radical.

Table VI: Effects of Galvinoxyl on Decomposition of XII

Compound	moles/mole perester	
	perester alone	perester with Galvinoxyl
carbon dioxide	1.55	1.01
di-*t*-butyl carbonate	0.37,0.44	0.35
C_4-hydrocarbons	0.24,0.27	<0.03

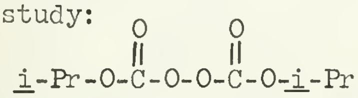
It is apparent from the rate and product studies that di-*t*-butylmonoperoxyoxalate (XII) decomposes with the concerted fission of two bonds. Its high rate of decomposition must therefore be due to the inherent weakness of the carbon-carbon oxalate bond.

That XII decomposes almost three times faster than di-*t*-butyldiperoxyoxalate (IV) strongly indicates that IV decomposes by the two bond mechanism also. What need to be explained are the relative rates of decomposition of IV and the monoperoxyoxalates. A resonance form such as II, which was used by Bartlett and Rüchardt to explain the substituent effects in the phenylperacetates, will not adequately explain the large difference in rates between IX-a and XII. The *t*-butyl ester decomposes 16 times faster than the ethyl ester. This suggested to Bartlett, Gontarev and Sakurai that the cationic stability of the R group is important in the transition state, and they pictured a charge separated transition state as in XIII. Such a transition state could explain the 16-fold greater decomposition rate for XII than for IX-a. However, these workers feel that, due to the symmetry of IV and the polar nature of the *t*-butoxy group, the high rate of decomposition of IV cannot be explained using the mechanism for the decomposition of the monoperoxyoxalates unless the *t*-butoxy group in IV brings about a direct weakening of the carbon-carbon oxalate bond.

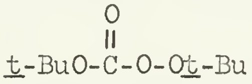

XIII

This ground state destabilization in IV does not seem necessary, however. A transition state such as XIII can explain the relative rates of decomposition of all of these peresters. Although the radical contributor to XIII would be more important for di-*t*-butyldiperoxyoxalate (R = *t*-BuO) than its counterpart in di-*t*-butylmonoperoxyoxalate (R = *t*-Bu), the ionic contributor to XIII could be sufficiently more important in the latter to swing the decomposition rate in its favor. The relative ineffectiveness of the benzyl group is in accord with the finding that benzylic type resonance is also not as important as might be expected in substituted peracetates.[11] *t*-Butyl phenylperacetate has an enthalpy of activation only 2.1 kcal. lower than that of *t*-butyl trimethylperacetate (27.9 kcal. compared to 30.0 kcal.), although the "resonance energy" of the benzyl radical is 24.5 kcal. compared to 12 kcal. for the *t*-butyl radical.[23] These "resonance energies" were determined by comparing the carbon-hydrogen dissociation energies of *t*-Bu-H (90 kcal./mole) and ϕCH_2-H (77.5 kcal./mole) to that of CH_3-H (102 kcal./mole).

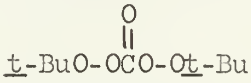
The Peroxycarbonates - The following three peroxycarbonate esters have received kinetic study:


$\underline{i}\text{-Pr-O-}\overset{\overset{O}{\|}}{C}\text{-O-O-}\overset{\overset{O}{\|}}{C}\text{-O-}\underline{i}\text{-Pr}$

XIV

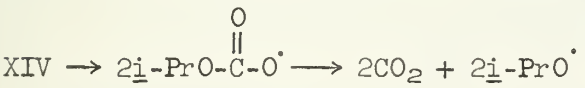

$\underline{t}\text{-BuO-}\overset{\overset{O}{\|}}{C}\text{-O-O}\underline{t}\text{-Bu}$

XV


$\underline{t}\text{-BuO-O}\overset{\overset{O}{\|}}{C}\text{O-O}\underline{t}\text{-Bu}$

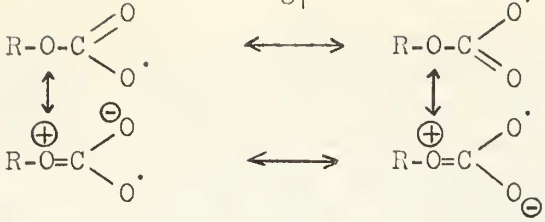
XVI

The kinetics and products of decomposition of di-isopropyl peroxydicarbonate (XIV) have been determined.[24] When XIV was decomposed in ethylbenzene at 50°, the products were: CO_2, 88%, 1.76 mole per mole XIV; isopropyl alcohol, 59%; *meso*-2,3-diphenylbutane, 21%. When XIV was decomposed in ethylbenzene with added styrene, the yields of CO_2 and isopropyl alcohol fell to 11% and 5%, respectively. These results point to a mode of decomposition that involves the initial cleavage of the peroxidic oxygen-oxygen bond, producing two isopropyl carbonate radicals (XVII). In the presence of styrene, the isopropyl carbonate radicals (XVII) are trapped by the styrene before they decompose to isopropoxy radicals and CO_2. That the isopropyl carbonate radicals (XVII) live long enough to be trapped by the styrene indicates that they are more stable than acetoxy radicals. This greater stability probably derives from the resonance forms shown on the next page.[25]


$\text{XIV} \rightarrow 2\underline{i}\text{-PrO-}\overset{\overset{O}{\|}}{C}\text{-O}^{\cdot} \longrightarrow 2CO_2 + 2\underline{i}\text{-PrO}^{\cdot}$

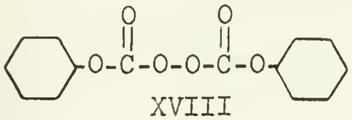
XVII

Strain found the first-order rate constant for XIV in toluene at 50° to be 0.109 hr.$^{-1}$, corresponding to a half-life of 6.3 hr.[26] The half life of benzoyl per-

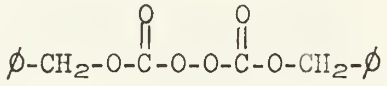


oxide at 50° calculated from Bartlett's data is 430 hr. The activation energy was found to be 28.1 kcal./mole.

Russian workers have determined the activation energies for dicyclohexyl peroxydicarbonate (XVIII) and dibenzyl peroxydicarbonate (XIX) in various solvents.[27] The activation energy for XVIII in benzene is 29.7 kcal. The values for XIX in benzene, dibutylphthalate and isopropyl alcohol are 31.8 kcal., 32.1 kcal. and 26.8 kcal., respectively. The lower value for the activation energy in isopropyl alcohol suggests that induced decomposition was occurring.



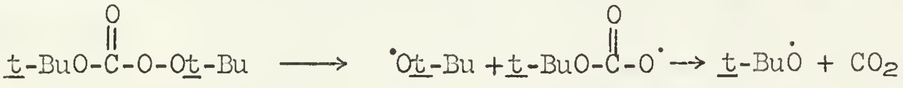
XVIII



$$\phi\text{-CH}_2\text{-O-}\overset{\overset{O}{\|}}{C}\text{-O-O-}\overset{\overset{O}{\|}}{C}\text{-O-CH}_2\text{-}\phi$$

XIX

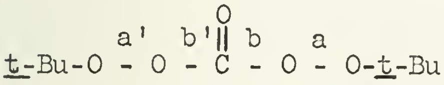
The kinetics and products of decomposition of di-*t*-butylmonoperoxycarbonate (XV) were investigated by Bartlett and Sakurai.[19] The decomposition of XV in cumene at 100° gave a quantitative yield of CO_2, and the *t*-butyl group was fully accounted for in the 1.93 mole of *t*-butyl alcohol and 0.13 mole of acetone formed per mole of XV. The activation parameters were determined from kinetic runs made in the temperature range 100 - 122°. The values are $\Delta H^{\ddagger}$= 35.4 kcal. and $\Delta S^{\ddagger}$= 14.6 e.u. The low rate ($t_{1/2}$ at 60° is 2×10^6 min.) and high enthalpy of activation indicate that the first step in the decomposition is the rupture of the oxygen-oxygen bond.



$$t\text{-BuO-}\overset{\overset{O}{\|}}{C}\text{-O-O}t\text{-Bu} \longrightarrow {}^{\bullet}\text{O}t\text{-Bu} + t\text{-BuO-}\overset{\overset{O}{\|}}{C}\text{-O}^{\bullet} \longrightarrow t\text{-Bu}\dot{\text{O}} + CO_2$$

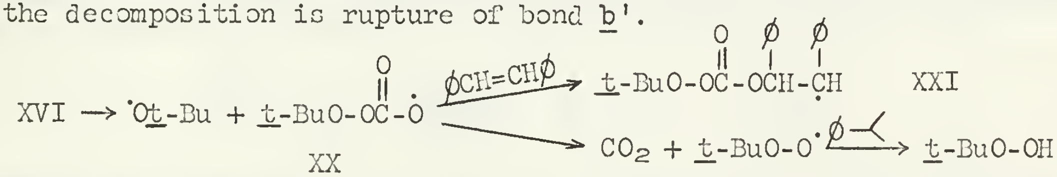
XV

The mechanism of the decomposition of di-*t*-butyldiperoxycarbonate (XVI) has been investigated by Martin.[25] This compound offered some interesting possibilities. If bonds *a* and *a*' cleaved, either stepwise or in concert, the hypothetical CO_3[28] would be formed. If bonds *a* and *b*' cleaved, then a nonperoxidic (*b*') bond would have broken in preference to a peroxidic bond (*a*'). The activation parameters were found to be: $\Delta H^{\ddagger}$= 31.8 kcal., $\Delta S^{\ddagger}$= 7.1 e.u. Decompositions in the presence of cumene at 110° gave quantitative yields of CO_2. When XVI was decomposed in the presence of *trans*-stilbene, the yield of CO_2 fell to 72%. From this it was concluded that the initial step of the decomposition is the rupture of bond *a*, producing *t*-butylperoxycarbonate radical (XX) and *t*-butoxy radical. In the presence of *trans*-stilbene, the radicals (XX) are partially trapped by the stilbene producing XXI. When the decomposition was carried out in cumene, *t*-butylhydroperoxide was isolated as its *p*-nitrobenzoate derivative. This was taken as evidence that the peroxidic bond *a*' remains intact and that the second step of the decomposition is rupture of bond *b*'.



$$t\text{-Bu-O} \overset{a'}{-} \text{O} \overset{b'}{-} \overset{\overset{O}{\|}}{C} \overset{b}{-} \text{O} \overset{a}{-} \text{O-}t\text{-Bu}$$

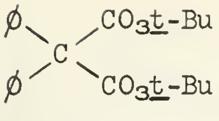
XVI



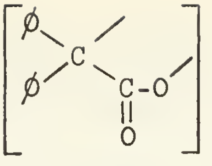
XXI

XX

Miscellaneous Peresters - Bartlett and Gortler have studied the decomposition of di-*t*-butylperoxy diphenylmalonate (XXII).[29] XXII was investigated to see whether this perester could, with the elimination of two CO_2 molecules either in a concerted or stepwise fashion, produce diphenyl carbene. When XXII was decomposed in cyclohexene, no evidence for the formation of a cyclopropane was found, and it was observed that an incomplete loss of CO_2 had occurred. Product studies in cumene showed that only 50%

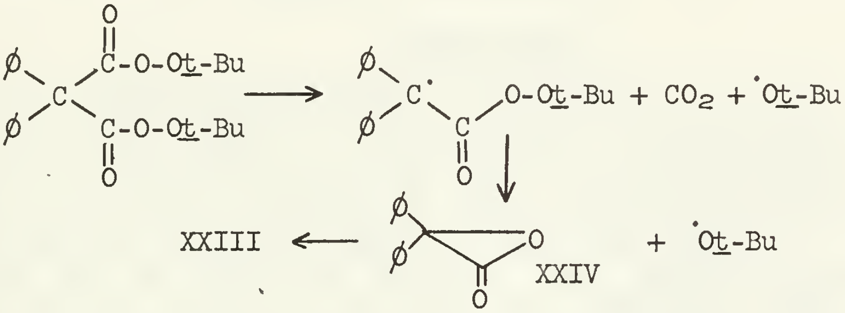


XXII

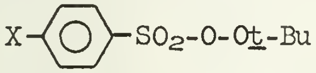


XXIII

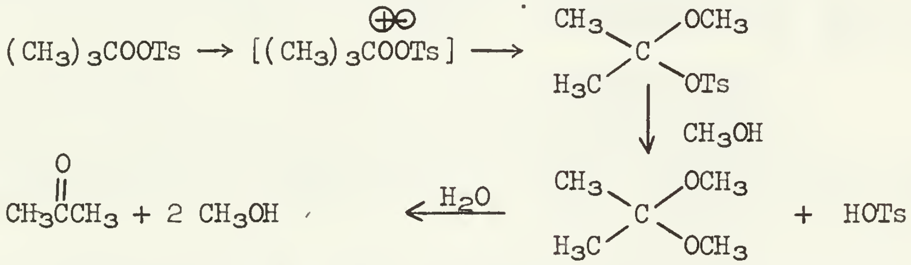
of the maximum amount of CO_2 had been produced, but the *t*-butyl groups were accounted for in the *t*-butyl alcohol and acetone formed to the extent of 90%. A polymeric material was isolated from the cumene solution, and this polymer was found to be identical to the polyester of benzilic acid (XXIII), which had been earlier reported by Staudinger.[30] From the high rate of decomposition ($t_{1/2}$ at 70° = 4 min.; $\Delta H^{\ddagger}$= 25.8 kcal./mole, $\Delta S^{\ddagger}$= 4.8 e u.), it was apparent that XXII decomposes with the concerted loss of a molecule of CO_2. The following scheme involving an α-lactone (XXIV) was proposed to account for the formation of XXIII. The large amount of strain present in XXIV could furnish the necessary driving force for polymerization.



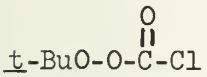
Bartlett and coworkers have found that *t*-butyl peresters of strong organic acids show a tendency to decompose by ionization of the oxygen-oxygen bond rather than by homolysis. The decomposition of *t*-butyl trifluoroacetate without solvent produces only a 3.1% yield of CO_2, the major products being trifluoroacetic acid (69%) and trifluoroacetic esters (28%).[10] These products point to an ionic rearrangement of the type first discovered by Criegee for 9-decalyl perbenzoate.[31] Similar ionic decompositions have been reported for the *t*-butyl arylpersulfonates (XXV).[32,33] The mechanism proposed for this decomposition is shown below.



XXV



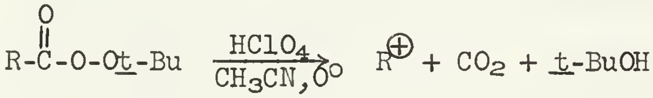
The mechanism of the decomposition of *t*-butylperoxy chloroformate (XXVI) was found to vary with the solvent.[34] In cumene XXVI decomposes with the concerted loss of CO_2. The half-life at 60° is 104 min. However, when the solvent is formic acid, ionic rearrangement of the Criegee type occurs.



$\underline{t}\text{-BuO-O-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-Cl}$

XXVI

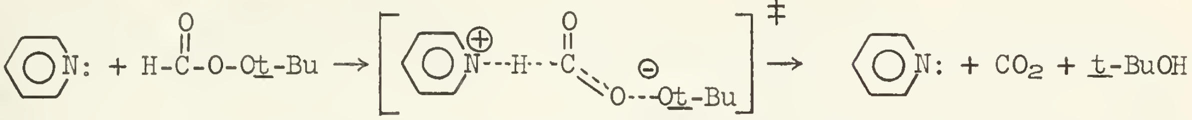
An example of an ionic perester fragmentation reaction was reported by Rüchardt.[35,36] The reaction is of the type where R=cycloheptatrienyl and di-n-propylcyclopropenyl. However, no structural evidence was given for these peresters.



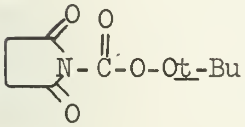
$$\text{R-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-O-O}\underline{t}\text{-Bu} \xrightarrow[\text{CH}_3\text{CN},0^\circ]{\text{HClO}_4} \text{R}^{\oplus} + \text{CO}_2 + \underline{t}\text{-BuOH}$$

t-Butyl performate (XXVII) is another example of a perester whose mode of decomposition is solvent dependent. Decomposition in chlorobenzene at 140° proceeds homolytically with the formation of formyloxy and *t*-butoxy radicals.[37] The activation parameters ($\Delta H^{\ddagger}$= 38 kcal./mole, $\Delta S^{\ddagger}$= 15 e.u.) indicate that this is the most stable perester of its class. However, when XXVII was decomposed in chlorobenzene in the presence of a small amount of pyridine, a huge increase in the rate of decomposition was observed.[38] The activation parameters for this base-catalyzed reaction were found to be:

$\Delta H^{\ddagger} = 15.3$ kcal. mole, $\Delta S^{\ddagger} = -23$ e.u. The products of the reaction were almost quantitative yields of CO_2 and *t*-butyl alcohol. In addition, a huge dependence of the rate of this catalyzed reaction on solvent polarity was noted. The authors proposed the following mechanism to explain these observations:



Recently, the decomposition of *t*-butyl N-succinimidepercarboxylate (XXVIII) has been investigated independently by two groups of workers.[39,40] It was found that XXVIII decomposes by an ionic mechanism in chlorobenzene and benzene but by a homolytic pathway in cyclohexene.



XXVIII

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THE REACTION OF DI-t-BUTYL PEROXIDE WITH SIMPLE ALKYL, BENZYL AND CYCLIC ETHERS

Reported by R. L. Keener November 12, 1964

INTRODUCTION: Ever since Gomberg's preparation of the triphenyl methyl radical in 1900[1], the free radical chemistry of organic compounds has been a topic of numerous and extensive investigations. Many excellent reviews on the free radical chemistry of organic compounds are available[2,3,4,5].

Progress in completely describing specific free radical reactions has normally been a slow process owing to the unusual and complex reaction paths which usually characterize homolytic reactions. While the study of the homolytic reactions of ethers may be considered as having begun in the 1940s with the discovery of the nature of the 'induced' decomposition of benzoyl peroxide in ethers[6,7], few significant studies were reported between that period and the late 1950s.

Since the latter period however, a vast amount of work has been published concerning the free radical reactions of ethers. The studies have been conducted on many types of ethers and have employed a wide range of radical initiators. Due to the large amount of work in this field and to the seemingly ambiguous results that arise from the use of different free radical initiators, the scope of this paper has been limited so as to include only the reaction of ethers with di-t-butyl peroxide (t-Bu_2O_2). This particular initiator has been chosen since the majority of studies have employed this reagent and because the reactions initiated by di-t-butyl peroxide are generally less complicated by side reactions than those in which other free radical initiators are employed[3].

Moreover the scope of this paper excludes the studies of the homolytic reactions of unsaturated ethers, such as the vinyl and acetylenic ethers, and all other studies on ethers which contain additional functional groups.

STUDIES ON THE DECOMPOSITION OF DI-t-BUTYL PEROXIDE: The thermal decomposition of t-Bu_2O_2 to produce two t-butoxy radicals initially is well known and has been shown to follow a first order decay rate in both the gas phase and in solution[3,5]. The photochemical reaction gives similar results in solution[8a]. Frey has reported[8b] that 11% of the t-Bu_2O_2 decomposes to give two t-butyl radicals and oxygen when the pure liquid is irradiated with ultraviolet light at 17°. Moreover, Rust and co-workers[8c] have reported that the thermal and photochemical decomposition of pure liquid t-Bu_2O_2 produces isobutylene oxide and that the t-Bu_2O_2 under these conditions shows an induced decomposition.

The secondary decomposition of t-butoxy radical in the gas phase and in inert solvents is reported to yield acetone and free methyl radicals[3,5,8]. If the decomposition of the t-butoxy radical occurs in a solvent (R-H) which is a good hydrogen atom donor, the t-butoxy radical may abstract a hydrogen atom from the solvent to form t-butyl alcohol and a solvent radical. The ease of abstraction will depend on steric factors as well as on the difference in bond dissociation energies of bonds formed and broken[3,5]. The amount of hydrogen abstraction relative to decomposition of the t-butoxy radical will be dependent on the difference in activation energies for the two competing processes. The activation energy for the formation of two t-butoxy radicals from t-Bu_2O_2 is ca. 38 kcal. and the activation energy for the decomposition of t-butoxy radical to acetone and free methyl radicals is ca. 15 kcal..[3,5].

Brooks and co-workers[9a] have shown that the relative reactivities of C-H bonds toward t-butoxy radicals can be measured by determining the ratios of t-butyl alcohol to acetone produced in the reactions. If other contributions to the t-butyl alcohol and acetone concentrations are negligible, than the the t-butyl alcohol: acetone ratio will be directly proportional to the ratio of the rate of hydrogen abstraction to the rate of decomposition of t-butoxy radical. Using this method, these authors[9a] obtained results from a study on numerous hydrocarbon solvents which were consistent with predicted relative C-H bond reactivities. Representative $\frac{t\text{-BuOH}}{\text{acetone}}$ ratios found were: benzene (0.015), toluene (2.8), mesitylene (7.4), cyclohexane (18) and decalin (18). This method has been applied successfully by other workers[9b,9c].

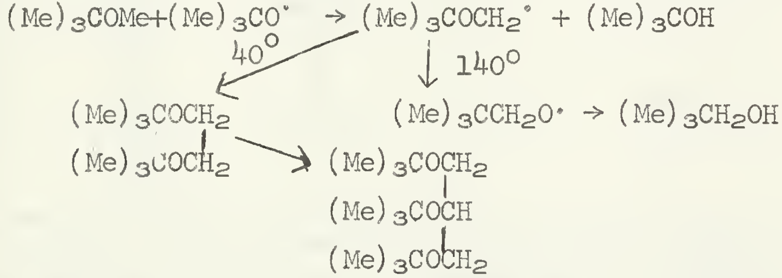
Since it had been previously assumed that only acyl peroxides undergo an induced decomposition in such solvents as alcohols and ethers, a mechanism involving the addition of an intermediate solvent radical to a carbonyl bond of the acyl peroxide had been proposed to account for the induced decomposition[3]. Recently however, Huyser and co-workers have reported that an alkyl peroxide, t-Bu_2O_2, undergoes an induced decomposi-

tion in some alcohols, and they proposed a direct attack on the O-O linkage of the peroxide by an α-hydroxy radical to account for the induced decomposition[10]. It is of interest however that no induced decomposition was observed when t-Bu_2O_2 was decomposed in tetrahydrofuran[10].

REACTION WITH ACYCLIC ETHERS: With the exception of McDonnell's work[11] in 1954, few reports have appeared concerning the reaction of simple alkyl ethers with t-Bu_2O_2. McDonnell reported that the reaction of t-Bu_2O_2 and di-n-butyl ether in the presence of 1-octene resulted in the addition of the ether to the olefin at the carbon atom adjacent (α) to the oxygen atom of the ether. As expected, the results indicated that the ether initially suffers hydrogen atom abstraction at the α-carbon position to give an α-etheral radical, which then adds to 1-octene. McDonnell also reported that the α-etheral radical partially decomposed to give butyraldehyde and n-butyl radical which added to 1-octene to produce 4-dodecanone and dodecane, respectively. This type of decomposition will be considered in more detail later in this paper.

The reaction of t-Bu_2O_2 with t-butyl methyl ether has recently been reported by Henbest and co-workers[12]. This paper is of further interest in that it illustrates the differences in reaction paths when the t-Bu_2O_2 is decomposed thermally and by photolysis. Using a 10:1 molar ratio of ether:peroxide and after allowing the thermal (140°) reaction to go to completion, the authors reported the major identified products to be t-butyl alcohol (93%), acetone (2%) and neopentyl alcohol (18%) as indicated by v.p.c. The ether was reported to be unchanged at 140° in the absence of peroxide.

The photo-initiated reaction at 40° using a mercury arc lamp (2570 A), yielded 1,2-di-t-butoxyethane (45%) and 1,2,3-tri-t-butoxypropane (11%) as major products. t-Butyl alcohol (unspecified yield) and a trace of neopentyl alcohol were also reported. The following reaction scheme was proposed to account for the products observed:



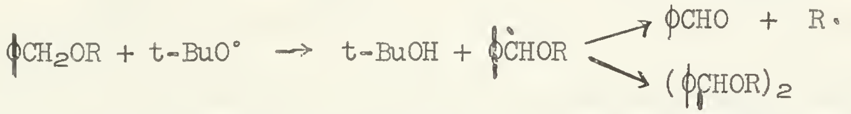
The alkyl migration proposed by the authors for the formation of neopentyl alcohol is unusual in that alkyl migrations are rare in free radicals and in the fact that alkyl group migration from O to C appears to be unprecedented. The authors themselves concede that such a step might be endothermic from a consideration of bond strengths. The possibility of decomposition of the initial ethereal radical into formaldehyde and a t-butyl radical, followed by a rapid recombination to yield the corresponding alkoxy radical was considered unlikely since no di-t-butyl ether was detected from either reaction. However, other studies have shown that alkyl radicals do add to formaldehyde and other carbonyl compounds[13,14], so that the possibility of a rapid recombination in preference to dimerization can not be completely dismissed. The contrasting results of the thermal and photochemical reactions may indicate that the lower temperature of the photochemical reaction does not provide the necessary activation energy for the rearrangement reaction, and consequently, the less energetic process of dimerization occurs. The authors reported that the contrasting results for the two reactions were expected on the basis of an earlier study[15].

In this earlier study, Henbest and co-workers[15] studied the reaction of t-Bu_2O_2 with anisole under conditions identical to those described above for t-butyl methyl ether. The major products from the thermal reaction were an isomeric mixture of methoxytoluenes (29%) and a similar mixture of phenoxymethylanisoles (12%). t-Butyl alcohol and acetone (1.64:1) were obtained in 90% yield, as was an unidentified resin. The photochemical reaction produced 1,2-diphenoxyethane (11%) and phenoxymethylanisoles (2%). No acetone was detected as a product from the latter reaction and the yield of resin was considerably less. The authors attributed the difference in reaction products from the two reactions to a greater rate of nuclear substitution in the thermal reaction and to the higher activation energy for nuclear substitution relative to that for dimerization in the photochemical reaction.

Due to an insufficient number of studies on the reaction of t-Bu_2O_2 with simple alkyl

ethers and to the rather inconclusive nature of those which have been reported, no generalizations on this topic are warrented at this time. However, much work has been reported within the last few years concerning the reaction of t-Bu_2O_2 with benzyl ethers. Two of these studies [16,17] have shown that the reaction path followed by the α-ethereal radical derived from the ether, ϕCH_2OR, is dependent on the nature of the R group.

The overall reaction scheme of benzylic ethers with t-Bu_2O_2 is described below;



$$\phi CH_2OR + t\text{-}BuO^{\circ} \longrightarrow t\text{-}BuOH + \phi\dot{C}HOR \begin{cases} \nearrow \phi CHO + R\cdot \\ \searrow (\phi CHOR)_2 \end{cases}$$

In the first study[16], a series of seven benzylic ethers were allowed to react under relux (115°-120°) for 96 hours and the reaction products isolated and identified. The products and yields are presented in Table I. The results show that when R=ϕCH_2 or ϕ_2CH, decomposition only occurs to produce benzaldehyde and the radical R$^{\cdot}$, while when R=ϕ or CH_3, dimerization alone occurs. When R=C_2H_5, i-C_3H_7 or t-C_4H_9, both reaction paths are followed. If it is assumed that the amount of decomposition (to produce ϕCHO and R$^{\cdot}$) relative to dimerization of the etheral radical decreases with the decreasing stability of the radical R$\cdot$ produced, then the order of stabilities of the radicals R$\cdot$ would be: ϕ_2CH, $\phi CH_2 >$ i-pr $>$ Et $>$ Me, ϕ. The t-butyl radical was not compared, since steric contributions to the decomposition could not be estimated.

TABLE I. PRODUCTS FROM THE REACTION OF t-Bu_2O_2 WITH BENZYL ETHERS.

	Reagents (mmoles)		Products (mmoles)			
R	Ether	t-Bu_2O_2	ϕCHO	ϕCO_2H	$(\phi COOCH\phi)_2$	$(\phi CHOR)_2$
ϕCH_2	130	70	33	14	2	--
Me	200	100	trace	--	-	33
Et	230	110	12	1	-	15
i-Pr	120	140	20	1	-	9
t-Bu	100	50	8	3	trace	5
ϕ	140	140	trace	-	--	31
ϕ_2CH	90	90	"	3	--	*

Assuming that the relative stability of the radical produced from decompostion of the ethereal radical is the determining factor in the degree of decomposition, then the yields of the isolated products are in agreement with theory[3]. However, these results in themselves can not be used as proof of the relative stabilities of the radicals R$\cdot$, owing to the rather poor yields of the relevent products.

In a later paper[7], Huang and co-workers reported a similar study on five additional benzylic ethers and two alkyl ethers. The results of this investigation are listed in Table II. and, in general, are in agreement with the predicted results. However, the interpetation of these results is also subject to the same limitations as discussed above for the previous study on benzylic ethers. Several additional observations on this latter study, however, are in order. Firstly, the reactions in this study were carried out by heating the peroxide and ether in a sealed bomb for 24 hours at 125°. Secondly, it was found that when R= s-butyl, cyclopentyl or cyclohexyl in the benzylic ether ϕCH_2OR, there is appreciable hydrogen abstraction from the tertiary carbon atom in R to produce, after decomposition of the intermediate radical, 2-butanone, cyclopentanone and cyclohexanone, respectively. The yields of the recovered products indicated that the extent to which the latter type of hydrogen atom abstraction occured in these three benzylic ethers was in the order: cyclopentyl $>$ cyclohexyl, s-butyl. Products arising from this type of hydrogen abstraction were not reported in the previous study.

TABLE II. PRODUCTS FROM THE REACTION OF t-Bu_2O_2 WITH ETHERS

Ether	Ether, mmoles	Peroxide, mmoles	Cleavage products, mmoles				Intractable oils (g)
			Ph·CHO	BzOH	Ketone	Dimer	
$(Ph\cdot CHMe)_2O$	120	30	---	--	COPhMe 18.0*		(2.3)
$Ph\cdot CH_2\cdot O\cdot CH_2\cdot CH_2\cdot Ph$	170	43	1.0	0.01		5.0	(4.1)
$Ph\cdot CH_2\cdot O\cdot$s.Bu	230	53	10.5	1.0	COMeEt 6.5	27.1	(3.5)

$Ph\cdot CH_2\cdot O\cdot C_5H_9$	100	25	5.9	--	Cyclopentanone	meso 4.2 Rac. 5·0	(0·6)
$Ph\cdot CH_2\cdot O\cdot C_6H_{11}$	130	33	4.7	--	Cyclohexanone	meso 7·0 Rac. 3.2	(0·5)
$C_6H_{11}\cdot O\cdot t\cdot Bu$	130	30	--	--	,, 8·2		(3·5)
$C_6H_{11}\cdot OMe$	450	113	---	--	,,14·3	11	(6.6)

* Also isolated, 2,3-diphenylbutane in the meso- (1.0 g., 5 mmoles) and racemic form (0.62 g, 3 mmoles).

Earlier studies on substituted toluenes[18], aliphatic acids[19] and aromatic aldehydes[20] indicated that polar effects may be important in hydrogen atom abstraction reactions when the abstracting radical is of fairly high electronegativity. Consequently, Huang and co-workers[21,22] investigated polar effects of the substituent X in the benzylic ethers $X\text{-}\phi\text{-}CH_2OCH_2\phi$ (X=p-Cl, p-MeO, p-t-Bu, m-Cl and p-Me) on the abstraction of a hydrogen atom from the benzylic carbon atom of the substituted benzene ring in the dibenzyl ethers. The results, shown in Table III, were obtained by isolating the substituted benzaldehydes and benzoic acids as derivatives.

If the polar resonance form shown below is important in the transition state for the

$$R\text{-}H\ X' \longleftrightarrow \overset{+}{\overbrace{R\cdot H}}\ \overset{-}{X:} \longleftrightarrow R^{\cdot}\ H\text{-}X$$

removal of a hydrogen atom from a donor (R-H), then one would expect electron releasing groups in R to facilitate the abstraction (relative to X=H) and electron withdrawing groups to hinder it. While the results in Table III show that hydrogen atom abstraction is facilitated when X=p-t-Bu, p-MeO and p-Cl, the relative values for the p-MeO and p-t-Bu substituted ethers indicate that a linear polar effect is not operative. Likewise, the value for the m-Cl substituted ether does not support a linear relationship. Because of the latter two observations and because some of the results reported in this study are in conflict with those reported in another paper[22], no unambiguous conclusions can be drawn from this study concerning the nature or importance of polar effects in hydrogen atom abstraction from benzylic ethers by t-butoxy radicals.

TABLE III. SUBSTITUENT EFFECTS ON THE CLEAVAGE OF SUBSTITUTED DIBENZYL ETHERS BY $t\text{-}BU_2O_2$

	REAGENTS (m. moles)			PRODUCTS (% yield)	
X	Ether Used	Ether reacted	Ether / Peroxide	% Yield %ϕCHO	% Yield of XϕCHO and XϕCOOH
p-Me*	95	53	2:1	13	26
p-t-Bu*	91	41	5:1	8	63
p-MeO*	92	38	5:1	8	51
m-Cl*	110	55	5:1	40	41
p-Cl*	110	42	5:1	12	33
p-Cl**	170	35	2:1	14	57

* Sealed tube under N_2 at 110 for 96 hours.

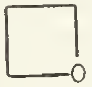
** Open vessel at 110-115 for 38 hours.

In a later paper[22] Huang repeated his study of the reaction of monosubstituted dibenzyl ethers with $t\text{-}Bu_2O_2$. The reactions this time were carried out by refluxing a 10:1 mole ratio of ethers:peroxide at 110° for 46 hours under argon. The aldehyde products were identified by v.p.c. and by their 2,4-dinitrophenylhydrazone derivatives. The molar ratios of XϕCHO:ϕCHO for X=m-Cl, p-Cl and p-t-Bu were 0.65, 1.2 and 1.2 respectively. Neglecting the p-Cl value, Huang reported a ρ value for the hydrogen atom abstraction by t-butoxy radicals to be -0.5. From similar studies with benzoyl peroxide, he reported a value for the abstraction by benzoyloxy radical of -0.6. The high reactivity for the ether with X=p-Cl was left unexplained. In view of this fact and the fact that the Hammett plot was made from the results of studies on only two of the ethers investigated, the value assigned by Huang for the reaction with t-butoxy radical must be considered only tentative.

It is pertinent to note that Russel and Williamson[23] have recently reported that the autoxidation of benzyl phenyl and benzyl alkyl ethers by azo-bisisobutyronitrile is insensitive to the nature of the substituent in either the benzyl or phenyl groups. These authors proposed that the insensitivity observed was due to the strong electron

releasing effect of the ether oxygen and to the decreased electron affinity of the peroxy radical relative to the t-butoxy radical.

REACTION WITH CYCLIC ETHERS: Gritter and Wallace[24,25] have recently investigated the reactions of $t\text{-}Bu_2O_2$ with the simple cycloalkyl ethers, trimethylene oxide (I), tetrahydrofuran (II) and terahydropyran (III). The reactions were carried out at 135-140°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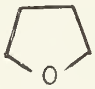
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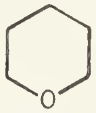

III

in the presence of 1-octene and the products identified by v.p.c. analysis. The results shown in Table IV shows that ketones and substituted ethers were the major products identified in the reaction mixtures; with the ketones being the predominant products. Telomers were also reported to have been formed.

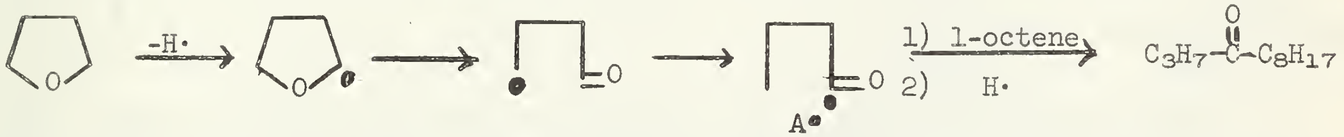
TABLE IV

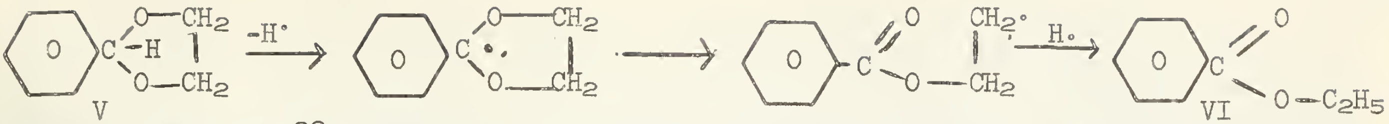
REACTION CONDITIONS USED AND PRODUCTS ISOLATED FROM THE CYCLIC ETHERS STUDIED

Reactant (moles)	1-Octene, moles, % conv.	tert-Butyl percxide mole	Time., hr. Temp., deg.	Product %yield,[a] conv.%[b]	Residue g.,mol.wt.
Tetrahydrofuran (1.3)	0.25, 52	0.03	2 150	4-Dodecanone 41,79	6,475
Tetrahydrofuran (2.0)	0.20, 35	0.06	5 150	4-Dodedanone and 2-octyltetrahydrofuran 12, 67	18.1
Tetrahydrofuran (0.626)	0.32	0.0003	24 135	4-Dodecanone and 2-octyltetrahydrofuran	
Tetrahydrofuran (0.626)	0.0604	0.0003	24 135	4-Dodecanone and 2-octyltetrahydrofuran	
Tetrahydropyran (1.5)	0.20, 79	0.06	2 150	5-Tridecanone 39, 49	9
Tetrahydropyran	0.154, 40	0.03	2 150	5-Tridecanone and 2-octyltetrahydropyran 10, 25	5.5
Trimethylene oxide	0.20, 25	0.03	2 145	3-Hendecanone 14, 65	19,578

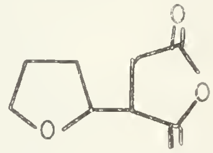
[a] Based on the total amount of 1-octene used. [b] Based on the amount of 1-octene converted to product.

Two mechanisms were proposed to account for the products formed. The first involved abstraction of a hydrogen atom from the α-carbon atom of the ether, followed by decyclization and an intramolecular hydrogen atom transfer to give the radical A which then adds to 1-octene. The second proposal involved the attack of an intermediate free radical on the 2-octyl ether (formed by addition of the α-ethereal radical to 1-octene) to give an intermediate radical which then decyclized and chain transferred to give the ketonic products. The results of this investigation did not allow a decision to be made between the two proposed pathways. It is of interest, however, that Huyser and co-workers[26,27] had earlier proposed a mechanism, similar to the first one proposed above by Gritter, to explain the reaction products obtained from the reaction of $t\text{-}Bu_2O_2$ with cyclic acetals. He found that when 2-methoxytetrahyropyran was reacted with $t\text{-}Bu_2O_2$, methyl valerate (IV) was one of the major reaction products isolated[26]. Similarly, four different benzal derivatives were converted to their isomeric benzoate derivatives in good yield[27]. The proposed reaction scheme is illustrated below for the conversion of ethylene benzal (V) to ethyl benzoate (VI):

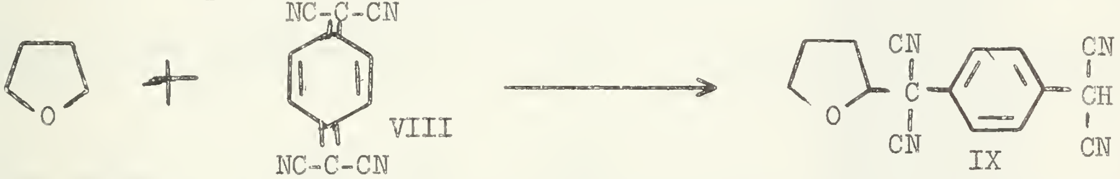




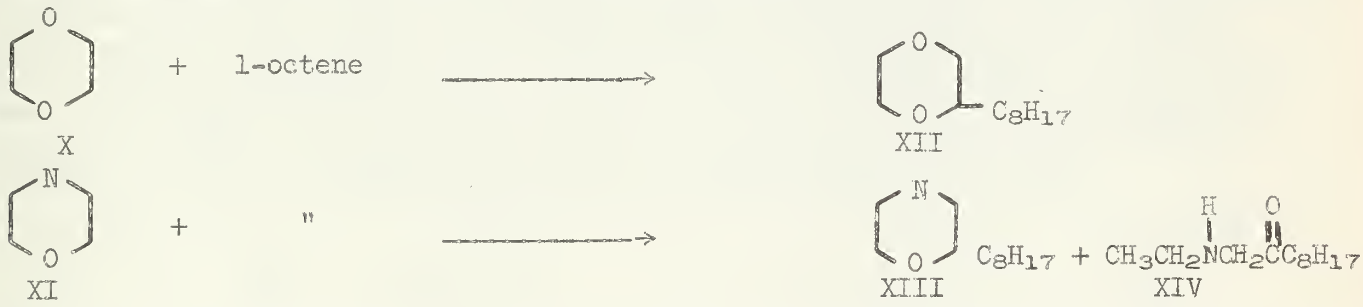
Jacobs and Ecke[28] found that when tetrahydrofuran is allowed to react with t-Bu$_2$O$_2$ at 70°, only traces of carbonyl compounds are produced and that most of the starting materials are recovered unchanged. The same reaction at 150° was reported above to produce 4-dodecanone in 41% yield. Jacobs and Ecke also studied the reaction of tetrahydrofuran with t-Bu$_2$O$_2$ in the presence of maleic anhydride at 70° and 150°. The reaction at 70° gave a 54-60% yield of (tetrahydro-2-furyl)succinic anhydride (VII), while the reaction at 150° produced VII in 42% yield. No products resulting from cleavage of the ethereal ring were observed, and the authors suggested that this was a result of the greater reactivity (relative to 1-octene) of the double bond in maleic anhydride.


VII

Diekmann and Pedersen[29] have also investigated the reaction of tetrahydrofuran with olefins initiated by t-Bu$_2$O$_2$ and by photolysis. They found that when THF, t-Bu$_2$O$_2$ and 7,7,8,8-tetracyanoquinodimethan (VIII) were heated at 150°, the adduct IX was produced in 33% yield. When THF and VIII were irradiated with a G.E. sunlamp, IX was formed in 55% yield. The structure assigned to the adduct IX was supported by i.r., u.v. and n.m.r. spectra. No ring opened products were reported.



The reactions of p-dioxane (X) and morpholine (XI) with t-Bu$_2$O$_2$ at 150° in the presence of 1-octene have also been reported[30]. p-Dioxane gave a 22% yield of the adduct XII and no ring opened products were reported. Morpholine gave an 8% yield of the adduct XIII and a 31% yield of the ring opened adduct XIV. The authors proposed that the apparent failure of p-dioxane to yield a ring opened adduct indicated that higher temperatures are required for the decyclization of the hypothetical p-dioxanyl free radical intermediate. The explanation was offered without proof. The results do indicate however that α-carbon-hydrogen bonds in cyclic ethers are more susceptible to hydrogen atom abstraction than those in cyclic amines. Gay[31] had reported earlier that less than 1% of amine radicals derived from cyclic amines undergo rearrangement.



The t-Bu$_2$O$_2$ initiated reaction of p-dioxane with trichloroethylene is reported to yield 1,1-dichloro-2-dioxanylethylene as the major product[32]. Again, no products resulting from cleavage of the ethereal ring were reported.

The t-Bu$_2$O$_2$ initiated reactions of epoxides with 1-octene have also been investigated by Gritter and co-workers[33,34]. The epoxides studied and the products reported are shown in table V. The results indicate that epoxides primarily undergo hydrogen atom abstraction at the tertiary carbon atom alpha to the oxygen atom. The authors proposed that these radicals then rearrange to produce the isomeric keto radicals which then add to 1-octene and chain transfer to form the ketones which were observed. This mechanism is the same as that proposed earlier for the higher cyclic ethers except for the fact that the keto radicals derived from the epoxides do not undergo intramolecular hydrogen transfer. The lower yield of ketones from the three-membered ring ethers was attributed

to the greater sp_2 character of the C-H bonds on the three-membered rings. The formation of 5-hydroxy-2-hexanone in the propylene oxide reactions was proposed to result from a radical displacement of the 1-C atom of propylene oxide by acetonyl radical to yield the resultant alkoxy radical, which could then be converted to 5-hydroxy-2-hexanone by abstraction of a hydrogen atom. In contrast to the ring-opened products observed by Gritter, Walling has reported the reaction of propylene oxide with t-butyl hypochlorite to yield mainly 2-chloropropylene oxide at 0° and 70° [35].

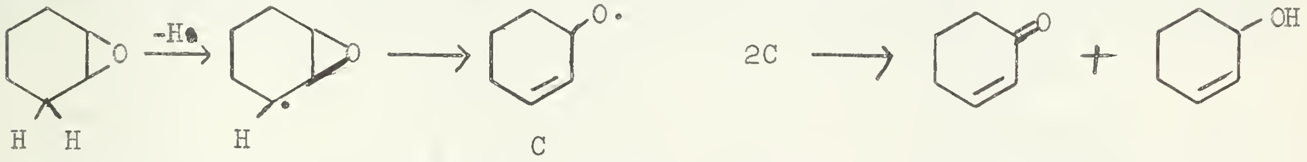
TABLE V. REACTION CONDITIONS USED AND PRODUCTS IDENTIFIED FROM THE EPOXIDES STUDIED

Epoxide (moles)	1-Octene (mole, %conv.)	t-Butyl peroxide (mole)	Time (hr) Temp.	(% Yield[a], conv.%[b])	Residue (g., mol. wt.)
1,2-Epoxyoctane (2.0)	0.40, 48.9	0.06	3 145°	7 hexadecanone (7,7,16.1)	10.1, 538
1,2-Epoxybutane (2.0)	0.40, 40.7	0.06	3 145°	3-dodecanone (4.2, 9.4)	25.3, 466
Propylene oxide (I) (3.0)	0.20, 0	0.015	17 125°	5-hydroxy-2-hexanone[c] (1.8)	2.3, 640
Propylene oxide (II) (2.0)	0.20, 39.3	0.03	2 150°	5-hydroxy-2-hexanone[c] (1.8) 2-hendecanone (3.2, 8.2)	11.2, 324
Propylene oxide (III) (2.0)	0.10, 50.8	0.12	1 200°	5-hydroxy-2-hexanone[c] (0.4) 2-hendecanone (23.4, 70)	10.2, 349
Styrene oxide	0.20, 23.6	0.03	3 150°	capriphenone (6.6, 28.4)	6

[a] Based on the total amount of 1-octene used. [b] Based on the amount of 1-octene converted to product. [c] Yield based on the amount of propylene oxide used.

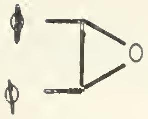
By using the method of Brooks (see page 70), Gritter and his co-workers attempted to determine the relative reactivities of various cyclic ethers with $t\text{-}Bu_2O_2$. While the results indicated that tetrahydrofuran and tetrahydropyran were of similar reactivity and of much greater reactivity than trimethylene oxide and propylene oxide, comparison of the latter two compounds strictly on the basis of ring size is not justified since the propylene oxide is a substituted ring compound and since later work[36] has indicated that epoxides may also undergo β-carbon hydrogen atom abstraction. The t-butyl alcohol: acetone ratios observed for tetrahydrofuran, tetrahydropyran, trimethylene oxide and propylene oxide were 5.10, 4.00, 0.57 and 0.45 respectively (see page 70).

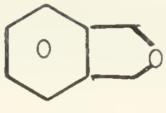
When cyclohexene oxide was heated with $t\text{-}Bu_2O_2$ at 150°, the products formed were cyclohexanone (32%), 2-cyclohexenone (9%) and 2-cyclohexenol (7%). The following scheme was proposed[36] to account for the cyclohexene derivatives formed:

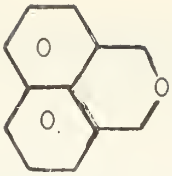


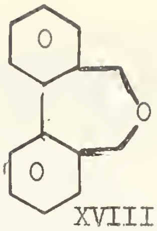
Cyclohexene oxide was found to be unreacted at 150° in the absence of $t\text{-}Bu_2O_2$. Moreover, the reaction of cyclohexanone with $t\text{-}Bu_2O_2$ at 150° produced no detectable products with C-C unsaturation. Unsaturated C-C products were also obtained from the reaction of propylene oxide and 1,2-butylene oxide with $t\text{-}Bu_2O_2$.

In order to determine the effect of steric factors on the reaction path of radicals derived from benzyl ethers, Huang and co-workers[37] have recently investigated the reactions of five cyclic benzyl ethers with $t\text{-}Bu_2O_2$ at 120-125°. The ethers investigated were cis- and trans- stilbene oxide (XV), phthalan (XVI), napthalan (XVII) and diphenan (XVIII).

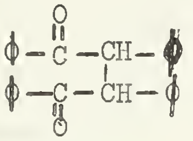

XV


XVI

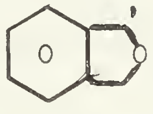

XVII


XVIII

The reaction with cis-XV gave a 57% yield of α,α-dibenzoylbibenzyl (XIX), the meso and racemic isomers being obtained in ca. equal yields. Trans-XV also gave the dimer but in much lower yield and in the meso form only. The reaction with trans-XV also led to the formation of much more polymer. The authors proposed that the high yield of dimer in the first case could be explained by a preferential attack of t-butoxy radical of cis-XV rather than on its more sterically hindered dimer. On the other hand, attack on the dimer formed from trans-XV would be expected to compete favorably with attack on the sterically hindered trans-XV. In agreement with the predicted relative degrees of attack, the t-butyl alcohol:acetone ratios for cis- and trans-XV were 5:1 and 0.8:1, respectively.



XIX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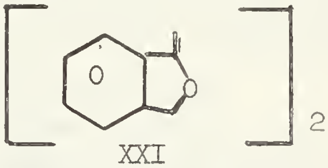
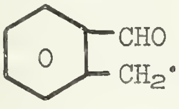
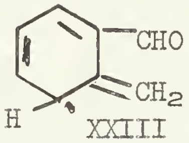

XXI

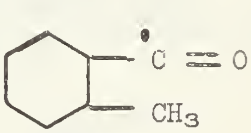
The radical XX, derived from phthalan, dimerised to give XXI, but no products were isolated which would be derived from the radical XXII produced from XX by cleavage of the ethereal linkage.



XXII



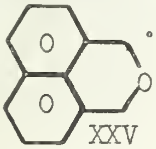
XXIII

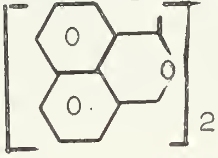


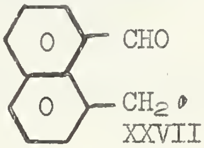
XXIV

The authors proposed that the failure os XX to undergo cleavage to XXII was due to the inability of XXII to be stabilized by resonance structures such as XXIII, owing to the unfavorable orientation of the =CH$_2$ group in such structures. In an attempt to support this argument, Huang and co-workers investigated the reaction of t-Bu$_2$O$_2$ with o-tolualdehyde. Since the bond dissociation energies of toluene and benzaldehyde are reported to differ by only 1 kcal[5], Huang proposed that hydrogen atom abstraction would occur preferentially from the 2-formyl group of o-tolualdehyde to give the radical XXIV which could be stabilized by resonance structures in which there were no unfavorable orientations as those described above. As predicted by Huang, the only products which were isolated from the reaction were those which would be derived from XXIV and not from XXII. However, the observed mode of attack in this reaction may be a reflection of steric factors in the attack of t-butoxy radical on the substrate and not necessarily a reflection of resonance contributions to the stabilization of the derived radical.

The radical XXV, derived from napthalan, dimerized to give two isomeric forms of XXVI, and no products were isolated which would be derived from XXVII. The authors again attribute the failure of XXV to undergo cleavage to steric inhibition of resonance.

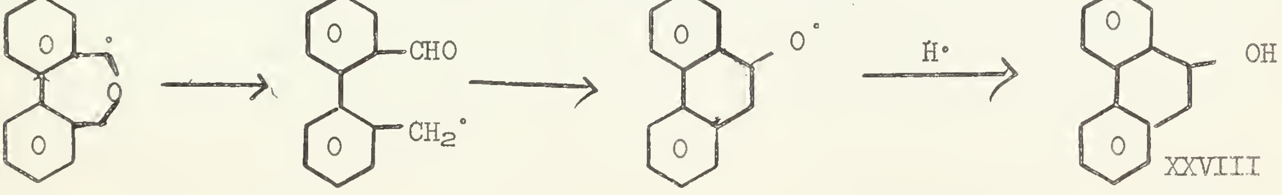

XXV


XXVI



XXVII

Interestingly, the reaction with diphenan gave 9,10-dihydro-9-phenanthrol (XXVIII) as the major product. Traces of other phenanthrene derivatives were also reported. The following mechanism was proposed for the formation of XXVIII:



XXVIII

A similar ring opening and closing mechanism has recently been proposed[38] for the epimerization of the steroid alcohol, 3β,20β-diacetoxy-11β-hydroxy-5α-pregnane, by lead tetra-acetate. Studies involving the addition of free alkyl radicals to carbonyl compounds were mentioned previously[13,14].

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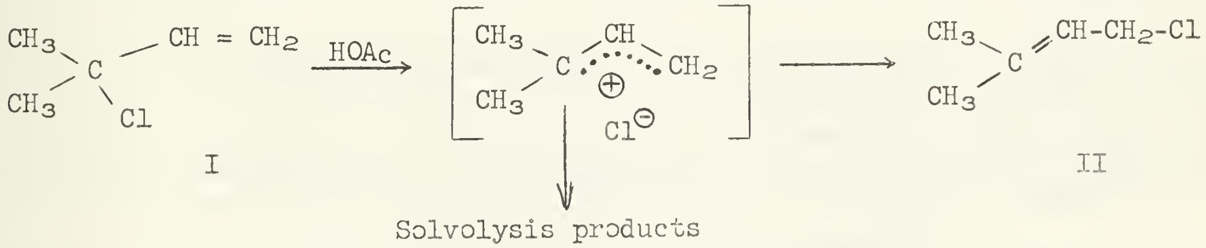
REARRANGEMENTS AND SOLVOLYSIS IN SOME ALLYLIC SYSTEMS

Reported by Jack Timberlake November 16, 1964

The possibility that a common intermediate was occurring between solvolysis and concomitant isomerization was first suggested by Winstein[1] in 1951. The acetolysis of α,α-dimethylallyl chloride (I) involved simultaneous solvolysis and intramolecular isomerization to γ,γ-dimethylallyl chloride (II). The instantaneous rate constant at constant ionic strength at 25° for acetolysis of I was calculated to be $15 \times 10^{-6} \text{sec.}^{-1}$ and decreased with time to a constant value of $2.2 \times 10^{-6} \text{sec.}^{-1}$, a value equal within experimental error to the first-order rate constant for acetolysis of γ,γ-dimethylallyl chloride (II), which remained constant with time. The fact that added chloride had no gross effect on the rate of solvolysis suggested the possibility that the reaction was intramolecular and was proceeding through a common intermediate.



More recent studies by Winstein[2] have indicated a need for a more plenteous scheme for carbonium ion reactions than one involving a single intermediate. Ionization of RX with rate constant k_1 gives rise to III, an intimate or internal ion

Scheme I

$$\begin{tikzcd} RX \arrow[r, shift left, "k_1"] & R^+X^- \arrow[l, shift left, "k_{-1}"] \arrow[r, shift left, "k_2"] & R^+||X^- \arrow[l, shift left, "k_{-2}"] \arrow[r, shift left, "k_3"] & R^+ + X^- \arrow[l, shift left, "k_{-3}"] \\ & III & IV \arrow[d, "k_s^{IV}"] & V \arrow[d, "k_s^{V}"] \\ & & ROS & ROS \end{tikzcd}$$

pair, which can undergo internal return to RX with rate constant k_{-1} or progress on to IV, a solvent separated ion pair. The solvent separated ion pair can undergo external ion pair return with rate constant k_{-2} or dissociate to V, dissociated ions, with rate constant k_3. Return from V is called external ion return. Broader terms, ion pair return and external return, are used to designate return from III and/or IV and from IV and/or V, respectively.

Conventional implements used in detection of the various types of ions are solvent effects, normal and special salt effects, common ion rate depression, anion exchange, and induced common ion rate depression.

Common ion rate depression[2] and exchange are most commonly used for detection of external ion return, although solvent separated ion pairs are capable of undergoing exchange with added external common ion.

From reaction scheme I, the first-order titrimetric solvolysis rate constant, k_t, is equal to $\frac{d(ROS)}{dt}/RX$. This expression upon steady state treatment yields:

$$k_t = k_1/1 + \frac{k_{-1}/k_2}{\left[k_s^{IV} + \dfrac{k_3 k_s^{V}}{k_{-3}(X^-) + k_s^{V}}\right] \Big/ \left[k_{-2} + k_s^{IV} + \dfrac{k_3 k_s^{V}}{k_{-3}(X^-) + k_s^{V}}\right]}$$

With this kinetic expression, an upper limit to the amount of rate depression by common ion X^-, where $k_{-3} \gg k_s^{V}$, can be predicted. k_t^d is defined as the fully depressed rate constant for the solvolysis.

$$k_t^d = k_1/1 + \frac{k_{-1}/k_2}{k_s^{IV}/(k_{-2} + k_s^{IV})}$$

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[R^+ + X^-\right] \xrightarrow{k_s^{iv}} ROS$$

$$-d(RX)/dt = k_1\left[\frac{1}{1 + \alpha(X^-)}\right] \quad \alpha = k_{-1}/k_s^{iv}$$

This is in contrast to the "mass law depression" derived by Hughes and Ingold[3] for the solvolysis of RX. In this case, k_t should continue to decrease as the concentration of X^- increases, and would eventually reach zero, a condition which Winstein did not observe.

In the acetolysis of 2-(2,4-dimethoxyphenyl)-ethyl p-bromobenzenesulfonate, k_t decreases gradually to a constant value, measured as the ratio of k_t at zero salt concentration to k_t at full depression. This ratio, k_t^o/k_t^d, was equal to 1.57. After the solvolysis rate constant reaches this minimum value, it is actually increased by further addition of common ion salt. This increase is ascribed to acceleration by normal salt effects.

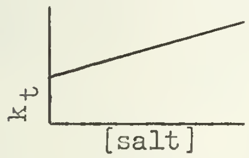
While external ion return must be present for the occurrence of common ion rate depression, i.e., its presence establishes at least some external return, its absence is not decisive. It will not be realized if $k_s^{iv} \gg k_3$, $k_s^V \gg k_{-3}(X^-)$ or $k_{-3}(X^-) \gg k_s^V$.

Exchange, on the other hand, does not require dissociation, since solvent separated ion pairs are sufficient for the phenomenon to be observed. The absence of exchange, however, permits the conclusion that external ion return is absent.

$$X^* + RX \rightleftharpoons R^+\|X^- \text{ or } R^+ + X^- \rightleftharpoons RX^*$$

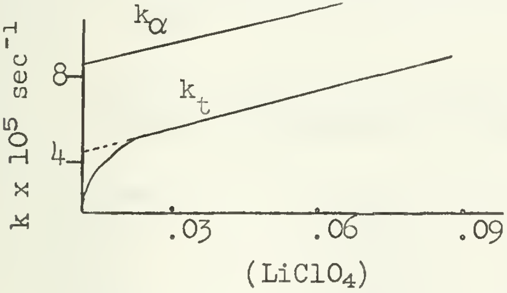
Threo-3-anisyl-2-butyl p-bromobenzenesulfonate shows no rate depression upon addition of lithium p-bromobenzenesulfonate. In fact, it shows a slight increase due to a normal salt effect, indicating an absence of common ion rate depression. It does, however, show a substantial decrease in rate when lithium p-toluenesulfonate is added. This is suggestive of exchange, as toluenesulfonates solvolyze slower than brosylates.

In a large number of ionic reactions, the addition of an inert salt causes a linearly increasing rate constant adhering to the equation $k_t = k_t^\circ\,[1+b(\text{salt})]$, where k_t° is the rate constant at zero salt concentration, k_t is the calculated rate constant at known concentration and b is the slope of the line.



In the acetolysis of optically active threo-3-anisyl-2-butyl p-bromobenzenesulfonate, Winstein[5] found the polarimetric rate constant to vary linearly with lithium perchlorate concentration. This normal salt effect was quite different from the salt effect on the titrimetric rate constant. The most salient effect of lithium perchlorate is an initial steep acceleration, termed special salt effect,[5,6,7] followed by a normal linear increase in the solvolysis rate constant.

Because of the atypical nature of the special salt effect, it is concluded that the effect is not one of generalized ion atmosphere but rather a direct reaction of lithium perchlorate with ion pairs in the solvent separated stage, thereby precluding ion pair return.



$$R^+\|X^- + LiClO_4 \rightleftharpoons R^+ClO_4^- + LiX$$

As added evidence to the existence of the solvent separated ion pair, Winstein[8] has observed induced common ion rate depression. The expected reversibility of such exchange as shown in the above equation suggests that addition of common salt M^+X^- should suppress the special salt enhanced rate, thus giving rise to induced common ion rate depression. Winstein has actually observed its concurrent existence with ~~all~~ systems that display special salt effects.

The reactions to be discussed here will be limited primarily to those thought to involve ionic pathways, although several examples with cyclic non-ionic pathways will

be discussed for purposes of comparison.

P.S. Smith[9], in a study of rearrangements of thiocyanates to isothiocyanates, found that allyl thiocyanate rearranged in a first-order manner to the corresponding isothiocyanate with nearly equal rates in a variety of solvents of differing polarity.

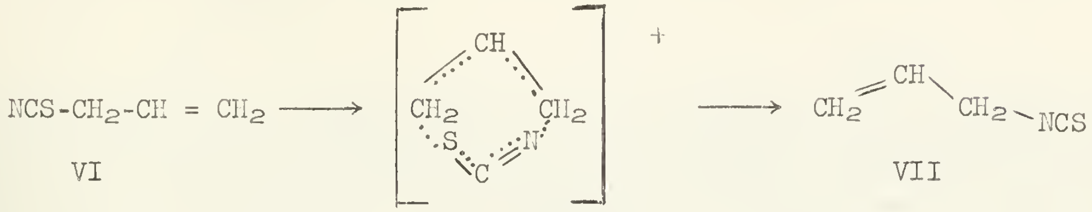
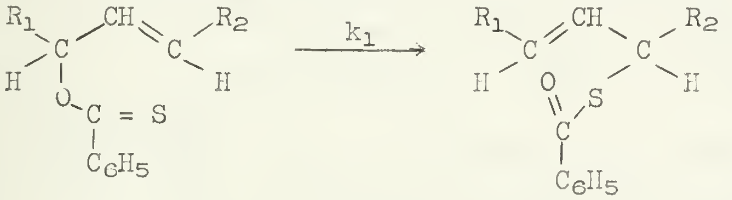

VI VII

TABLE 1

MEDIUM EFFECT ON THE RATE OF ISOMERIZATION OF ALLYL THIOCYANATE AT 68.2°

Solvent	Initial conc., mole/l.	k, hr^{-1}
Toluene	various	0.223
Nitrobenzene	0.826	0.233±0.008
Dimethyl formamide	0.408	0.199±0.004
Dimethylformamide with 0.40 M KSCN	0.404	0.193±0.003
Dimethylformamide with 0.398 M KI	0.404	0.190±0.007

The allylic rearrangement of allyl ($VIII_a$), crotyl ($VIII_b$) and α-methylallyl ($VIII_c$) thionbenzoates to thiolbenzoates has been studied in different solvents.[10] The slope obtained from plots of log $k_{reaction}$ versus log k for the rearrangement of p-methoxyneophyl toluenesulfonate in the different solvents gave a values[11] (solvent sensitivity parameters) equal to 0.13, 0.15 and 0.13 for $VIII_a$, $VIII_b$ and $VIII_c$, respectively. When contrasted to a reaction thought to involve a highly polar transition state, the rearrangement of cis-5-methyl-2-cyclohexenyl acid phthalate[12], a = 0.94[10], it is apparent that the rearrangement of these thionbenzoates undergoes only a small change in polarity in going to the transition state.


VIII IX

a R_1 = H R_2 = H

b R_1 = H R_2 = CH_3

c R_1 = CH_3 R_2 = H

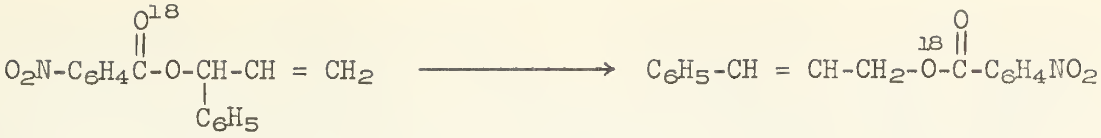
TABLE 2

REARRANGEMENT RATE CONSTANTS FOR SOME ALLYLIC THIONBENZOATES AT 100.0°

	10^4k_1, sec^{-1}		
Solvent	Allyl	Crotyl	α-Methylallyl
AcOH	0.567	3.72	30.7
MeCN	0.576	3.15	30.2
Me_2CO	0.273	1.81	16.6
C_6H_5Cl	0.224	1.27	13.8
$(CH_2)_4O$	0.218	1.20	12.0
C_6H_{12}	0.117	0.362	4.11

As internal and external return are permutable conditions and subject to change by alteration in substrate, leaving group, solvent and temperature, there is not always a sharp distinction between an ion pair and a covalently bound intermediate, and in some marginal cases, it would be possible to conceive of a reversal of mechanism when one or more of the aforementioned conditions are changed drastically.

It has been reported[14,15,16] that the isomerization of carbonyl labeled O^{18} α-phenylallyl p-nitrobenzoate (X) in chlorobenzene at 130° involves transfer of O^{18} from carbonyl to the ether position in the product, cinnamyl p-nitrobenzoate(XI).

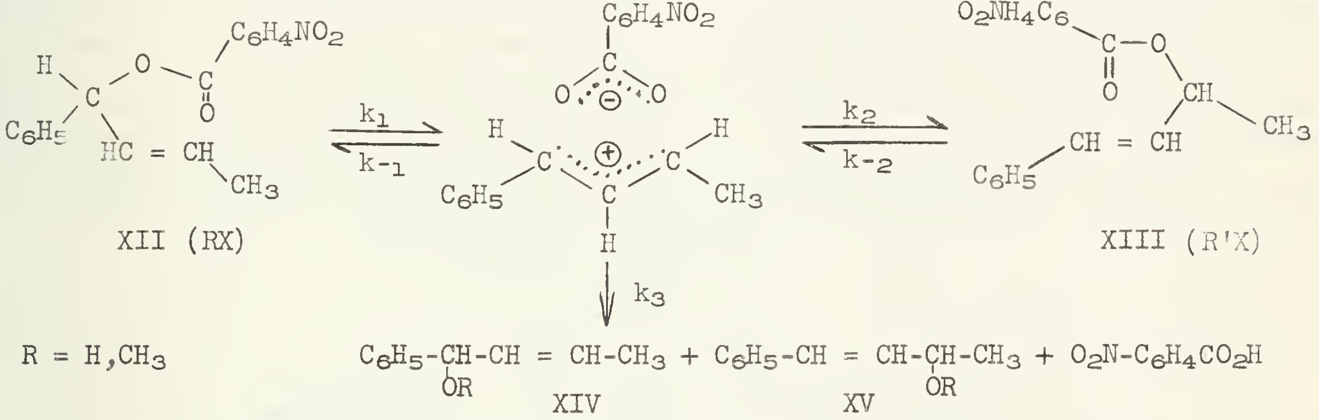


$O_2N\text{-}C_6H_4\overset{O^{18}}{\overset{\|}{C}}\text{-}O\text{-}\underset{C_6H_5}{\underset{|}{CH}}\text{-}CH = CH_2 \longrightarrow C_6H_5\text{-}CH = CH\text{-}CH_2\text{-}{}^{18}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}C_6H_4NO_2$

X XI

Similar results have been reported for the isomerization of α-phenyl-γ-methylallyl p-nitrobenzoate in benzene, acetone, acetic anhydride and acetonitrile.[13] From these data it was implied that in both cases a concerted mechanism was involved. As has been pointed out[5], however, these results do not exclude an ion pair intermediate, for in a non-polar solvent such as chlorobenzene, the intermediate, if an ion pair, would be expected to remain tightly bound. In fact, the results found by Doering on the α-phenyl-γ-methylallyl p-nitrobenzoate system when collated to those found by Sneen[17,18,19] are quite diagnostic of an ionic path.

By a combination of kinetic and ultraviolet spectrophotometric procedures, Sneen studied the concurrent solvolysis and rearrangement of α-phenyl-γ-methylallyl p-nitrobenzoate (XII) to γ-phenyl-α-methylallyl p-nitrobenzoate (XIII) in both methanol and 60% dioxane. The rate of solvolysis of XII relative to XIII in 70% dioxane was found to be ca. 300, a factor Sneen attributes to difference in ground state free energy.



The total rate of reaction of XII, k_{RX}, was found to be a combination of rate of rearrangement, k_R, and solvolysis, k_S. The rate constants for XII were calculated from $\frac{1}{t}\ln\frac{(HX_\infty)-(HX_0)}{(HX_\infty)-(HX_t)} = k_{RX}$, where (HX_∞) is the observed amount of liberated acid after 10 half-lives. Since for the α-aryl ester (XII), (HX_∞) is less than the theoretical amount of acid expected, it can be shown that the constant calculated from the above expression, k_{RX}, is a sum of the rate constants for two simultaneous first-order processes, acid-producing hydrolysis and rearrangement to the unreactive γ-aryl ester (XIII). To determine that XIII was stable under the conditions employed for determination of k_{RX}, infinity solutions from the reaction of α-phenyl-γ-methylallyl p-nitrobenzoate were transferred from the 25° constant temperature bath, after 10 half-lives, to one at 50°. The rate constants calculated in this manner agreed well with the ones calculated for the solvolysis of γ-phenyl-α-methylallyl p-nitrobenzoate.

Investigation of the solvolysis products by U.V. showed that the amount of XIV produced relative to XV was the same whether one started with XII or XIII. These results, coupled with the relatively large solvent sensitivities for the individual processes, were indicative of a common intermediate for both solvolysis and rearrangement. For the α-phenyl isomer XII, a change in solvent from 70% dioxane to 60% dioxane resulted in a 3.4 fold increase in rate for the rearrangement process with a corresponding m[20,21] value equal to 0.75. The hydrolysis process underwent a fourfold increase in rate and had an m value equal to 0.90. The m value is defined as the slope of the line determined by a plot of log $k_{reaction}$ versus Y value of the solvent. The Y value is a quantitative measure of a solvent's ionizing power, as manifested in its effect on the rate of solvolysis, and is defined by the relation $Y = \log \frac{k_{t\text{-}BuCl}}{k^{o}_{t\text{-}BuCl}}$. $k^{o}_{t\text{-}BuCl}$ is the

rate constant for the solvolysis of t-butyl chloride in the reference solvent, 80% ethanol, and $k_{t\text{-BuCl}}$ is the rate constant for the solvolysis in the given solvent.

The solvolysis of benzhydryl chloride in dioxane-water media, a reaction known to involve a carbonium ion intermediate[22,23] gives an m value of 1.05[24]. Thus, the parallel sensitivity of the solvolysis and rearrangement processes argues against a mechanism such as that proposed by de la Mare and Vernon[25] for the rearrangement of α,α-dimethylallyl chloride. They speculate that the rearrangement and solvolysis processes are two separate and unrelated reactions.

In order to gain insight into the type of ionic intermediate involved, the esters were allowed to react in the presence of varying amounts of sodium azide. Only normal salt effects were observed in the total rate of reaction for α-phenyl-γ-methylallyl p-nitrobenzoate, and since the amount of rearranged ester was not significantly changed, it was concluded that the azide ion entered the reaction at a later stage than that which determines the rate of reaction and the amounts of rearrangement products.

It was assumed in the product studies that the solvolysis products, once formed, were stable to the reaction conditions. This conjecture is probably unwarranted, as Winstein[26] has shown that α,α-dimethylallyl azide rearranges in a first-order manner and the equilibrium distribution shows little dependence on either solvent or structure. It appears that the process is thus cyclic and involves a relatively nonpolar transition state. The half-life of rearrangement in 70% acetone at 25° is 16 minutes. Since Sneen's product studies of α-phenyl-γ-methylallyl p-nitrobenzoate (XII), in 70% dioxane at 25°, were conducted after ten half-lives, 1,670 minutes, it may be reflected that the azide solvolysis products produced in the solvolysis of the allylic p-nitrobenzoates are equilibrium distributions and not absolute product percentages.

A final reaction scheme incorporating all the data can then be depicted as follows:

$$\begin{tikzcd}
 & RX \arrow[r, shift left, "k_1"] & R^+X^- \arrow[l, shift left, "k_{-1}"] \arrow[r, shift left, "k_{-2}"] \arrow[d, "k_s"] \arrow[dr, "k_{3s}"] & R'X \arrow[l, shift left, "k_2"] \\
RN_3 + R'N_3 & & R^+ + X^- \arrow[ll, "k_4(N_3^-)\,[N_3^-]"'] \arrow[r, "k_{4s}"] & ROS + R'OS
\end{tikzcd}$$

To show that solvent attack on R^+X^- cannot compete with dissociation, i.e., that $k_{3s}/k_3 \simeq 0$, the following equation was derived. A plot of the ratio of total solvolysis product to total alkyl azide vs. the reciprocal of the azide ion resulted in a straight line whose intercept was zero. It was therefore concluded that $k_{3s}/k_3 \simeq 0$ and that the solvent was incapable of attacking the intimate ion pair at a rate measurable to its rate of dissociation.

$$\frac{[ROS] + [R'OS]}{[RN_3] + [R'N_3]} = \frac{k_{4s}(k_{3s} + k_3)}{k_3 k_4(N_3^-)} \times \frac{1}{[N_3^-]} + \frac{k_{3s}}{k_3}$$

Some of the more interesting "limited" solvolysis reactions in allylic systems have been done by Goering on trans-α,γ-dimethylallyl and cis- and trans-5-methyl-2-cyclohexenyl chlorides, acid phthalates and p-nitrobenzoates. The substrates listed were chosen as suitable ones for probing into the mechanism of the ionization step. From all available data, the system can best be summarized as:

$$RX \underset{k_1}{\overset{k_\alpha}{\rightleftharpoons}} [R^+X^-] \xrightarrow{k_2} \text{solvolysis products}$$

Under conditions employed, aqueous acetone, it has been shown that at least the return step is intramolecular and stereospecific. Since accommodation of a return step from the dissociated stage is not consistent with the results obtained, it is believed that solvent completely intercepts the intermediate upon further ionization. However, it has been stated[27] that presumably dissociated carbonium ions and very possibly solvent separated ion pairs are intermediates in the product-forming step. As of yet, however, no work has been done which would elucidate the solvolysis step. Furthermore, in light of recent developments[23], it is the opinion of this author that additional evidence is needed in one of the three cases to establish unequivocally that return is only involved from an intimate ion pair.

From the above scheme the following relations are true:

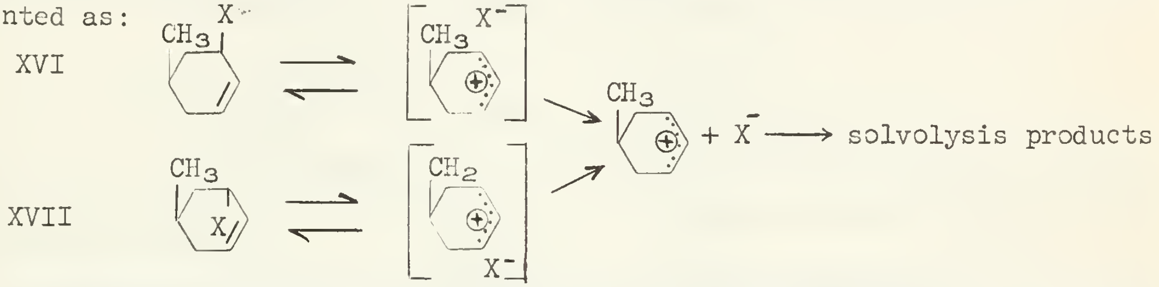
$$k_t = k_\alpha k_2/(k_1 + k_2)$$
$$k_\alpha/k_t = 1 + k_1/k_2$$
$$k_{rac} = k_\alpha - k_t$$

In these relationships k_t is the titrimetric rate constant, experimentally measurable by titration of the p-nitrobenzoic acid produced at different time intervals. When starting with optically active sub-

strates, k_α is the polarimetric rate constant and is a measure of rate of loss of optical activity as a function of time.

In the systems studied by Goering, solvolysis via a carbonium ion produces a symmetrical intermediate and return results in complete loss of optical activity. The excess loss of optical activity, i.e., the difference between k_α and k_t, is due to racemization of the unsolvolyzed material. The fact that return is occurring is exemplified by the greater rate of loss of optical activity, k_α, than rate of solvolysis, k_t. In all cases where additional complications by acid catalysis were not occurring, both k_t and k_α were first-order, and thus their difference, k_{rac}, was also first-order.

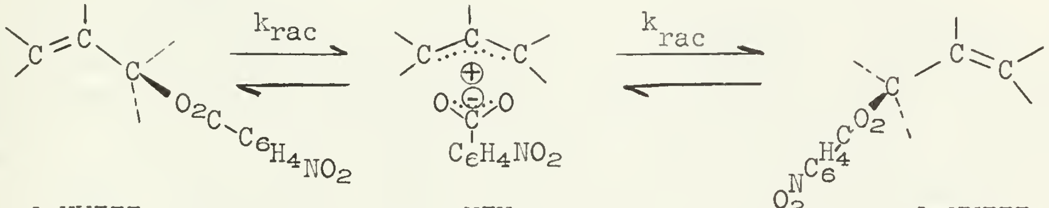
That external return in hydroxylic solvents is unimportant was shown by observing that no geometric isomerization occurred in the partial solvolysis of *cis*-and *trans*-5-methyl-2-cyclohexenyl acid phthalates.[28,29] Similar results were observed with the cyclohexenyl *p*-nitrobenzoates and *trans*-α,γ-dimethylallyl *p*-nitrobenzoate. The reisolated, unsolvolyzed esters, as indicated by infrared analysis, were exclusively of the same geometric configuration as the starting substrate. This allows the reaction to be represented as:



Further evidence that external return is absent is provided by a control experiment run on *dl*-*trans*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate-carbonyl-O^{18}. In this experiment 0.04 *M* ester (2.45±0.02 atom % excess O^{18}) was heated for 92.5 hours at 100° in 80% acetone containing 0.02 *M* sodium *p*-nitrobenzoate. This corresponds to about 47% racemization and 70% solvolysis. The O^{18} content of the recovered unsolvolyzed ester was 2.46±0.02 atom % excess. These results in this system rule out both solvent separated ion pairs and dissociated ions as sources of the rearrangement process.

These results differ from those found for the anionotropic rearrangements of *cis*- and *trans*-5-methyl-2-cyclohexenyl acid phthalates[30] in acetonitrile and in the fused state, and for the acid-catalyzed isomeric rearrangement of *cis*-and *trans*-5-methyl-2-cyclohexenols.[31,32]

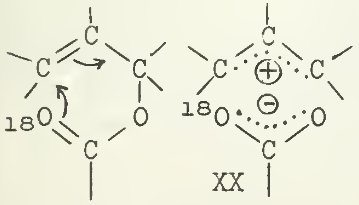
Since in aqueous acetone the rearrangement is intramolecular and does not involve isomerization, internal return therefore results in the interconversion of enantiomers.



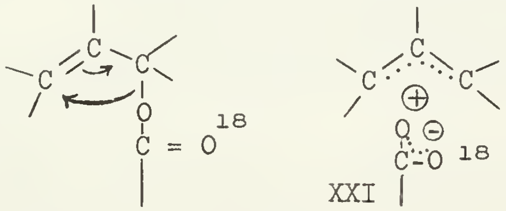
d-XVIII XIX *l*-XVIII

The rate constant, k_{rac}, corresponds to the rate of production of that fraction of the intermediate which returns to XVIII, and the rate constant for interconversion of the enantiomers is 1/2 k_{rac}.

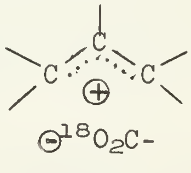
To gain additional insight into the nature of the bonding and the structure of XIX, oxygen equilibration of carbonyl-O^{18} labeled *d*-XVIII was studied. There are three possible relationships that can exist between reactant and rearranged product. They can be illustrated as:



XX



XXI



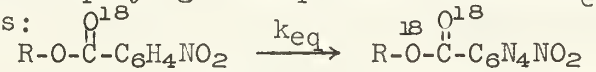
XXII

In the first of the illustrations, the intermediate (XX) is unsymmetrical with respect to the O^{18} atom. In the rearrangement, the carbonyl oxygen in one isomer becomes the ether oxygen in the other. In the second intermediate(XXI), which is also unsymmetrical,

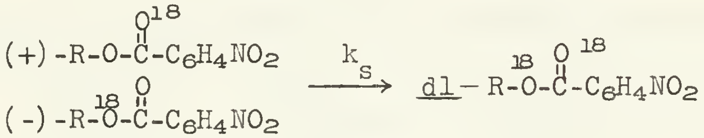
the ether oxygen in one isomer becomes the ether oxygen in the other. The O^{18} atom remains exclusively bonded in the carbonyl position. The final intermediate, (XXII), is completely symmetrical with respect to the O^{18} atom. It has an equal chance of being positioned in either isomer.

It is obvious that XXI can readily be distinguished from the other two, in that the ester will remain discretely labeled in the carbonyl position. The distinction between XX and XXII is more subtle, for as illustrated they represent limiting entities and there is the possibility that they will merge. However, the contribution of each can be determined by using an optically active labeled reactant and resolving the racemized unsolvolyzed ester and determining the O^{18} content of each position in each enantiomer. In the first limiting case the enantiomers would remain discretely labeled, the d-isomer in the carbonyl position and the l-isomer in the ether position. In the third possibility the d- or l- isomer would have both ether and carbonyl positions labeled.

The two rate constants employing O^{18} equilibration are $k_{equilibration}$ and $k_{scrambling}$ illustrated as:



$$R\text{-}O\text{-}\overset{O^{18}}{\overset{\|}{C}}\text{-}C_6H_4NO_2 \xrightarrow{k_{eq}} R\text{-}\overset{18}{O}\text{-}\overset{O^{18}}{\overset{\|}{C}}\text{-}C_6N_4NO_2$$



$$\begin{matrix}(+)\text{-}R\text{-}O\text{-}\overset{O^{18}}{\overset{\|}{C}}\text{-}C_6H_4NO_2 \\ (-)\text{-}R\text{-}\overset{18}{O}\text{-}\overset{O}{\overset{\|}{C}}\text{-}C_6H_4NO_2\end{matrix} \xrightarrow{k_s} \underline{dl}-R\text{-}\overset{18}{O}\text{-}\overset{O^{18}}{\overset{\|}{C}}\text{-}C_6H_4NO_2$$

The rate constants for the various processes for trans-α,γ-dimethylallyl p-nitrobenzoate are listed in Table 3.

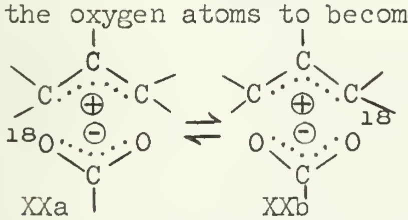
TABLE 3

KINETIC DATA FOR trans-α,γ-DIMETHYLALLYL p-NITROBENZOATE

Temp.	10^3hr^{-1} k_α	10^3hr^{-1} k_t	10^3hr^{-1} k_{rac}	10^3hr^{-1} k_{eq}	10^3hr^{-1} k_s	k_α/k_t	k_s/k_{rac}
			90% Acetone[33]				
99.61	22.8±0.3	4.23±0.01	18.6±0.3	17.9±0.6	6.4±0.3	5.4±0.1	0.34
			60% Acetone[34]				
59.94	20.4±0.3	9.42±0.05	11.0±0.3	10.6±0.2	4.6±0.2	2.17±0.1	0.42
99.61	1200	541					

From the table it is immediately obvious that in both 60 and 90% acetone $k_{eq}=k_{rac}$. Therefore both oxygen atoms in the anion XX and both carbon atoms are equivalent. Thus both k_{rac} and k_{eq} measure total internal return.

The rate of scrambling, k_s, relative to rate of racemization, k_{rac}, is also informative about the arrangement of atoms in the intermediate. If they are arranged as shown in XX, and there is a tendency to bond exclusively with the adjacent carbon atom, k_s will equal zero. If they are arranged as shown in XXII, k_s will be equal to k_{rac}. This would mean that both oxygen atoms are equivalent with respect to either carbon atom. However, if there is a tendency for the oxygen atoms to bond preferentially to the nearest carbon atom, k_s/k_{rac} will be less than unity. From examination of Table 3, it can be seen that the latter explanation appears to be the correct one. Thus in intermediate XX there appears to be a small energy barrier to be surpassed in order for the oxygen atoms to become equivalent with respect to each carbon atom. This is more readily understood when illustrated differently. For k_s/k_{rac} in 60% acetone the ratio is 0.42. This means that 42% of the product of internal return has the carboxyl oxygen atoms scrambled in each enantiomer or 21% of the enantiomers formed by internal return are inversely labeled. Furthermore, the equivalent oxygen atoms will prefer to bond with the nearest carbon atom 3.8 times faster than with the more remote one.



XXa XXb

The observed solvent effects on the various rates are consistent with the conjecture that a common intermediate, an intimate ion pair, is rate-determining for each process. In addition to this, it has been observed[34,35] that the ratio k_α/k_t is temperature independent. This likely would not be the case if the same intermediate were not involved for both processes. To substantiate the temperature independency, Goering

determined a value for k_t of 541 x $10^{-3}hr^{-1}$ at 100° in 60% acetone by extrapolation from data at lower temperatures. A value for $k\alpha$ was then calculated to be 1.2 hr^{-1}. A one point kinetic run agreed well with this calculated value for $k\alpha$.

The ratio k_s/k_{rac} has been proposed as a measure of the tightness of the ion pair. The fact that its variation is small, in changing from 90% acetone to 60% acetone, is to be expected from the Hammond activity postulate. "The intermediate (XX) is a relatively high energy species and the various transition states presumably resemble it in structure and polarity."[34]

For the rearrangement of cis-5-methyl-2-cyclohexenyl p-nitrobenzoate in 80% acetone at 100°, Goering[36] observed the following rate constants: $k\alpha = 2.39 \pm 0.04 \times 10^{-2}hr^{-1}$, $k_t = 1.37 \pm 0.04 \times 10^{-2}hr^{-1}$, $k_{rac} = 1.02 \pm 0.05 \times 10^{-2}hr^{-1}$, and $k_{eq} = 0.97 \pm 0.03 \times 10^{-2}hr^{-1}$. Thus $k_{eq} = k_{rac}$. Furthermore, it was found that within experimental error, k_s was also equivalent to the two preceding rate constants. This implies an intermediate best represented by XXII.

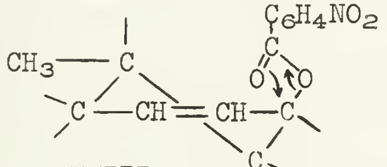
Even more disparity is observed in the case of trans-5-methyl-2-cyclohexenyl p-nitrobenzoate.[37]

TABLE 4

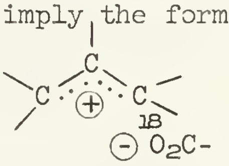
KINETIC DATA FOR trans-5-METHYL-2-CYCLOHEXENYL p-NITROBENZOATE

Temp.	$10^2k\alpha hr^{-1}$	$10^2k_t hr^{-1}$	$10^2k_{rac}hr^{-1}$	$10^2k_{eq}hr^{-1}$	$10^2k_s hr^{-1}$	$k\alpha/k_t$
			80% Acetone			
99.72	1.99±.07	1.30±.04	0.69	1.20	0.48	1.53
			60% Acetone			
99.72	23.7±.8	16.6±.3	7.2	10.5	3.4	1.43

Examination of Table 4 shows that for the trans-cyclohexenyl system $k_{eq} > k_{rac} > k_s$. From the previous discussion such results are certainly not expected. In its simplest form the rearrangement is illustrated by XIX. It is possible to conceive of the extreme case where $k_{rac} > k_{eq}$, as the intermediate could be represented by XXI. But never could k_{eq} exceed k_{rac}. Moreover, according to the usual criteria, exchange, kinetics, and solvent effects on both equilibration and racemization, it is apparent that both of these processes result from intimate ion pair return. The excess oxygen equilibration can be illustrated by XXIII. The results seem to imply the formation of an unsymmetrical ion pair (XXIV), in addition to a symmetrical one like XXII.

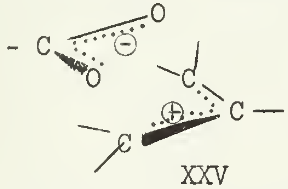


XXIII



XXIV

It is thought by Goering[36] that the favored transition state for the acyclic system is one of parallel exo orientation (XXV) and that for the cyclic systems this arrangement is sterically precluded. The reason for the different behavior in the isomeric 5-methyl-2-cyclohexenyl systems in not known.



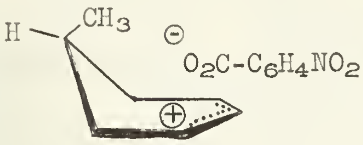
XXV

The results found by Goering seem to indicate that k_{eq} is a good measure of total ion return, possibly better than k_{rac}. It is interesting to note that for two symmetrical allylic systems, trans-5-methyl-2-cyclohexenyl and exo-(axial)bicyclo(3.2.1.)oct-3-en-2-yl[38] p-nitrobenzoates, k_{eq} exceeds k_{rac}.

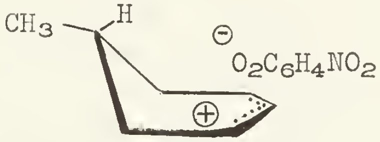
The use of k_{eq} as a reliable measure of total ion pair return has even been suggested for use in non-allylic systems and in "non-rearranging" systems. Its use appears to be documented by results found in solvolysis of p-chlorobenzhydryl p-nitrobenzoate in acetone. In this system, Goering[23] found $k_{eq}/k_{rac} = 2.3$. Furthermore, addition of sodium azide to the reaction reduced k_{rac} from 2.76×10^{-3} hr^{-1} to zero while only reducing k_{eq} by 9%, from $6.5 \times 10^{-3}hr^{-1}$ to $5.9 \times 10^{-3}hr^{-1}$. This shows that azide ion is capable of eliminating racemization, but not oxygen equilibration, and is compelling evidence that two intermediates are involved. There is one intermediate which returns with preservation of configuration and one which returns with racemization.

Of the three primary systems studied by Goering, the only one in which it was not

specifically mentioned that exchange with added anion was tried is the cis-5-methyl-2-cyclohexenyl p-nitrobenzoate. The possibility still remains that something slightly more removed than an intimate ion pair is involved, perhaps a solvent separated ion pair. Steric crowding of the methyl group is a possible explanation for the difference.



cis



trans

In the cis ion pair, steric repulsion of the methyl group moves the anion further from the positive center and further facilitates equilibration of the oxygen atoms.

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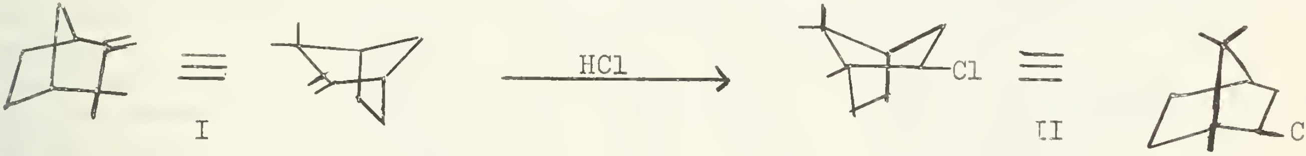
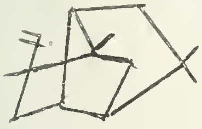
LONGIFOLENE

Reported by Michael A. Lintner November 19, 1964

INTRODUCTION

Longifolene ($C_{15}H_{24}$), an optically active ($[\alpha]_D=+42.73^\circ$) sesquiterpene, was first isolated in 1920 by Simonsen[1] through fractional distillation of Indian Turpentine from Pinus longifolia. Since then, it has been isolated from various other turpentine oils[2-19]. Longifolene reacts with halogen acids (except hydrofluoric acid) to give crystalline hydrohalides[1]. The relationship of the hydrohalides of longifolene with the parent hydrocarbon involves a Wagner-Meerwein rearrangement[20,21] in analogy with the conversion of camphene (I) to isobornyl chloride (II)[22]. Early work[23,24], reviewed by Barton and Simonsen[25], led to the proposal of two (III, IV) structures for longifolene. More recent work[21,26] has proven these structures to be incorrect, and by a combination of X-ray and chemical methods, structure V was shown to be correct. This work has been the subject of two brief reviews[27,28]. It is the purpose of this seminar to present a review of the structure proof and reactions of longifolene and to present the total syntheses of both dl and optically active longifolene.

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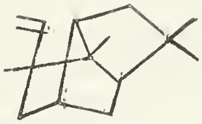
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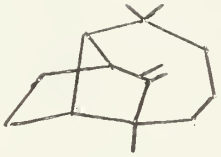

V

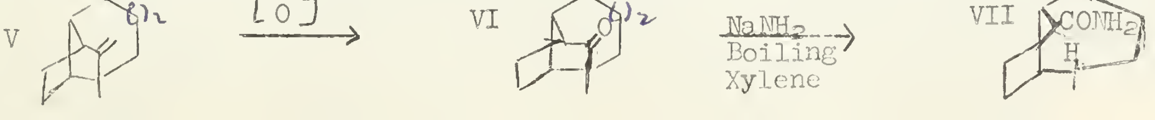
PROOF OF STRUCTURE

Longifolene, as the formula ($C_{15}H_{24}$) implies, has four double bonds or rings. Longifolene shows infrared absorption at 1664 cm^{-1} due to carbon-carbon double bond stretching[29], believed[30] to be due to a carbon-carbon double bond exocyclic to a cyclopentane system. It was hydrogenated, with difficulty, to take up one mole of hydrogen to give a saturated product[31]. Oxidation of longifolene gave two epimeric saturated acids ($C_{15}H_{24}O_2$) and this information, combined with the fact that the hydrohalides ($C_{15}H_{25}X$) were shown to be saturated[16,23], led to the conclusion that the three remaining sites of unsaturation were due to a tricyclic system.

It was then necessary to determine the nature of the carbon-carbon double bond. The isolation of formaldehyde from ozonolysis of longifolene showed the presence of a methylene group of the nature $RR'C=CH_2$ where R is alkyl and R' is either alkyl or hydrogen. The presence of bands in the infrared at 3077 cm^{-1} [30] and 877 cm^{-1} [16,30], while bands at 3010-3040 cm^{-1} [32] and 920 and 1000 cm^{-1} [33] were absent, showed the methylene group to be of the nature $>C=CH_2$. Final evidence that the carbon-carbon double bond is in a methylene group exocyclic to a cyclopentane ring was provided by the isolation of a monoketone from the ozonolysis. This ketone has infrared absorption, due to a cyclopentane carbonyl[34], at 1745 cm^{-1} [30].

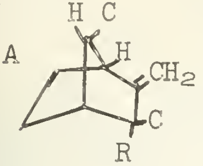
Vigorous oxidation of longifolene showed the presence of side groups. Drastic potassium permanganate oxidation[1] as well as nitric acid oxidation[23,24] gave assymmetric dimethylsuccinic acid and dimethylmalonic acid. Vigorous chromic acid oxidation gave acetone, identified as the 2,4-dinitrophenylhydrazone [16]. This evidence led to the deduction that a gem-dimethyl group was present as part of a $C-CMe_2-CH_2-C$ grouping.

Mild oxidation of longifolene (V) gave a monoketone VI[19,26,35,36,37] whose infrared spectrum showed absorption at 1745 cm^{-1} [26,30]. This ketone gave no carbonyl derivatives and was not attacked by selenium dioxide, bromine or cold aqueous potassium permanganate[26]. Treatment of VI with sodium amide in boiling xylene gave an amide ($C_{14}H_{25}NO$) whose structure was given as VII without evidence[26,35,36,37]. These reactions prove that the positions α to the carbonyl function are either fully substituted or bridgehead positions.



The similarity of these reactions to those of camphene (I) led to the proposal of partial structure A[26]. This proposal was supported by a comparison of the molecular rotation data of the (+)-longifolene series and (+)-longifolene hydrochloride to that of the (+)-camphene series and isobornyl chloride (table I). This analogy was supported by the fact that the trend of molecular rotations is the same and the magnitude of the shifts is the same[40].

A



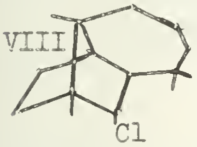
X-ray spectroscopy[21] established the structure of longifolene hydrochloride as VIII. The endo configuration of the chlorine atom is opposite to that of all prior known examples of conversion of camphenes to isobornyl derivatives and steric hindrance of this position to the accomodation of the chlorine atom was given as an explanation[26]. Since VIII could be formed via a Wagner-Meerwein rearrangement[20,21], by analogy with the formation of isobornyl chloride (II) from camphene (I)[22], Naffa and Ourisson were able to deduce the structure of longifolene as V[26].

TABLE I

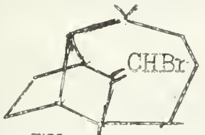
Molecular Rotation Data

(+)-Camphene Series	M	M	M	M	(+)-Longifolene Series
Camphene	+132	0	0	+92	Longifolene
ω-bromocamphene	+249	+117	+78	+170	ω-bromolongifolene
ω-nitrocamphene	+333	+201	+214	+306	ω-nitrolongifolene
Camphenilone	+97	-35	-133	-41	Longicamphenilone
Camphor	+65	-67	-44	+48	Longicamphor
Camphenic Acid	+5	-127	-178	-86	α-longifolic Acid
Isocamphane	-12	-144	-143	-51	Longifolane
Isobornyl Chloride	+57	-75	-76	+16	Longifolene Hydrochloride

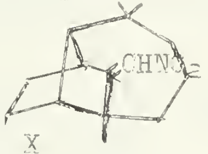
VIII



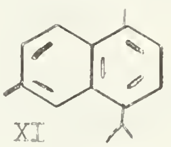
ADDITIONAL REACTIONS OF LONGIFOLENE. In addition to those discussed in the proof of structure, longifolene has undergone numerous interesting reactions. It reacted with bromine in the presence of N,N-dimethylaniline to give the vinylic bromide, ω-bromolongifolene (IX) and with "oxides of nitrogen" to give ω-nitrolongifolene (X)[16]. Selenium dehydrogenation of the hydrogenation product, longifolane, gave cadalene (XI)[31] while manganese dioxide-sulfuric acid oxidation of the original hydrocarbon gave trimellitic acid[24]. In the oxidation of longifolene several other products were isolated along with longicamphenilone (VI). An α-diketone (XII), shown by the formation of a quinoxaline[23], was one of the major products that was isolated[19,23,30,36,37,42]. A direct analogy can be drawn from the work of Hückel and Hartmann[41] in which camphene was converted in three steps to an α-diketone (XIII). This work was repeated by Naffa and Ourisson[35] using longifolene to give the observed α-diketone, longifdione. Longifdione (XII) was converted under Baeyer-Villager conditions[35] to an anhydride (XIV) which is also one of the products observed in the peracid oxidation of longifolene[35]. This anhydride was hydrolyzed to a dibasic acid, α-longiforic acid (XV)[35] which is also formed as a minor product in the peracid oxidation of longifolene and is the product when longifdione is cleaved by oxidation with nitric acid[23] or hydrogen peroxide[19,38,42]. This dibasic acid (XV) is epimerized in hydrobromic acid, converting to a β-isomer (XVI) which is characterized by its failure to form an anhydride[23]. Treatment of α-longiforic acid with selenium[37,42] or barium oxide[36] gave 4,8-dimethylazulene (XVII).



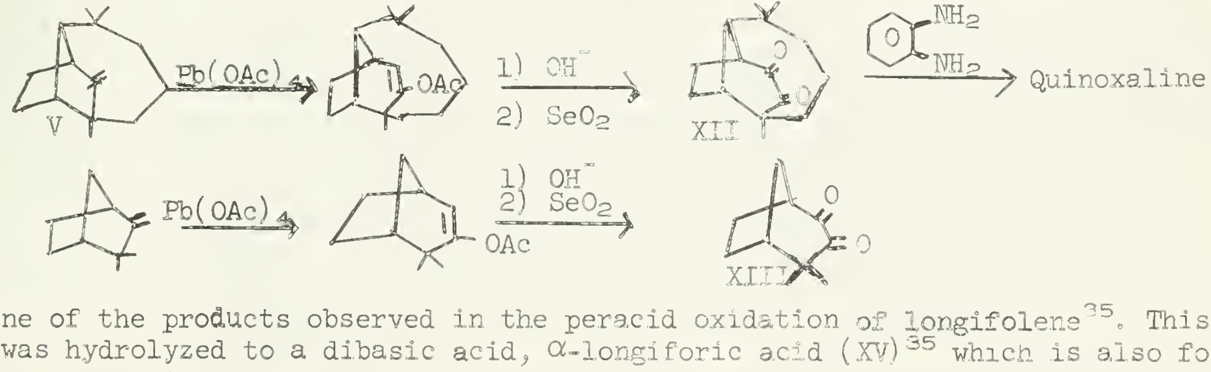
IX

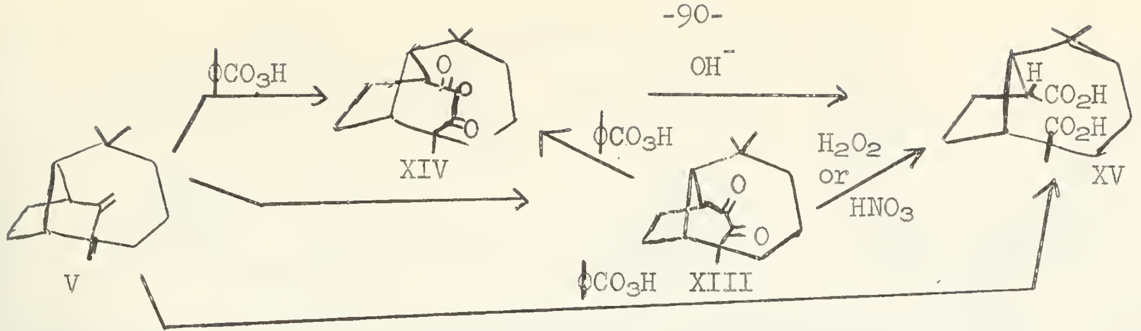


X

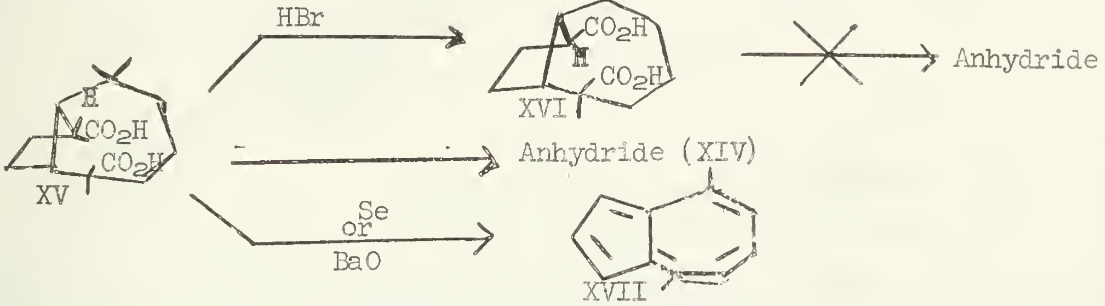


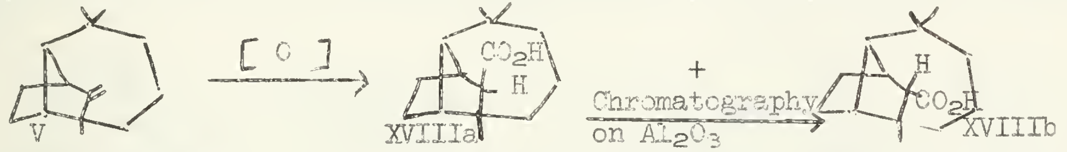
XI



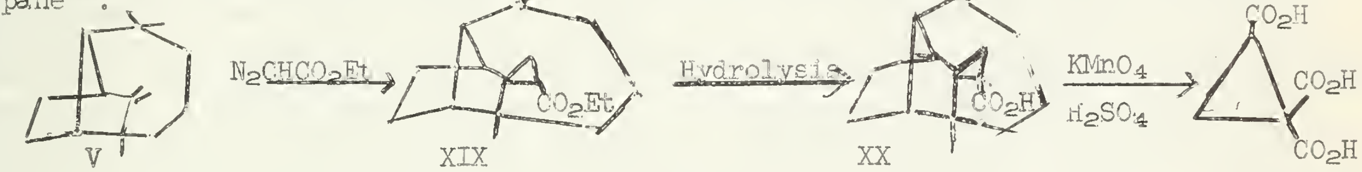


In addition to longifdione, anhydride (XIV) and α-longiforic acid, two epimeric monobasic ($C_{15}H_{24}O_2$) acids (XVIII a+b) are formed[19, 30, 43]. The methyl esters, when allowed to react with lithium aluminum hydride followed by phosphorus pentachloride, gave longifolene[30]. The acids can be separated easily since the methyl ester of longifolic acid (XVIIIa) is a liquid while that of isolongifolic acid (XVIIIb) is a solid[43]. Treatment of the pure ester with aqueous potassium hydroxide gave the pure acid[43]. Chromatography of longifolic acid on alumina converted it into its endo epimer[15].





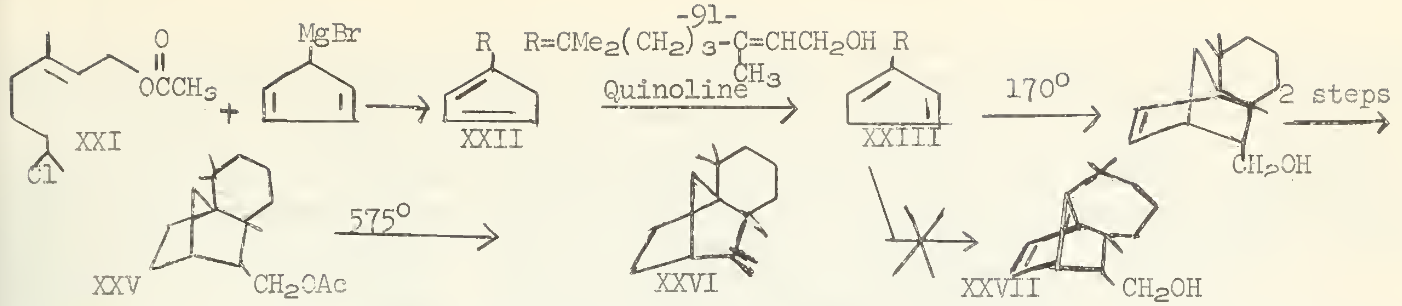
A most interesting reaction of longifolene is its reaction with ethyldiazoacetate to give the spiro compound (XIX). Hydrolysis of XIX gave the corresponding acid (XX) which was oxidized by potassium permanganate in sulfuric acid to give 1,1,2 tricarboxycyclopropane[36].



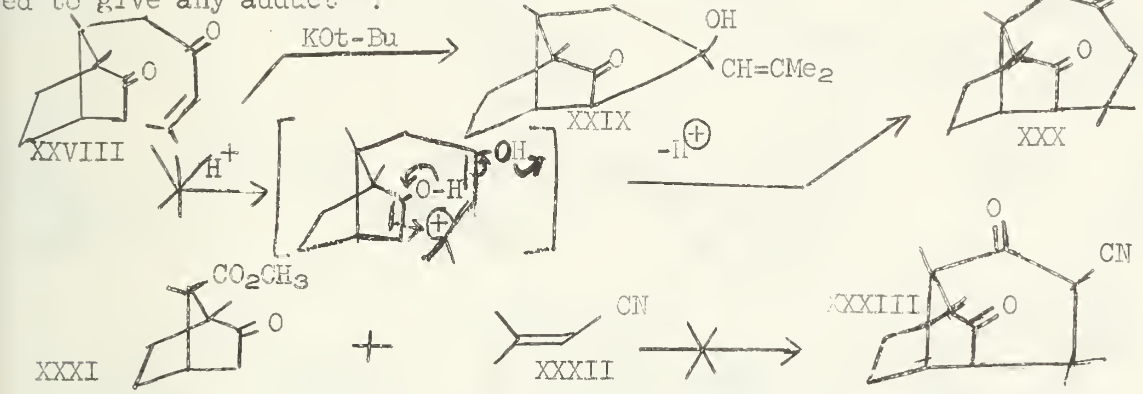
TOTAL SYNTHESIS OF *dl*-LONGIFOLENE AND (+)-LONGIFOLENE. The total syntheses of longifolene presented two major problems. The first was that of ring expansion to give the seven membered ring and the second, ring closure to give the tricyclic system. The ring expansion step will be discussed later in the paper.

In 1963, the Diels-Alder reaction was used in an attempt to obtain longifolene[53]. Geranylacetate hydrochloride (XXI) was allowed to react with the Grignard reagent derived from cyclopentadiene to give an oily product (XXII) having infrared absorption at 6.03 and 6.3μ. Isomerization of XXII in the presence of quinoline gave a crystalline product (XXIII) in which the infrared absorptions at 6.03 and 6.3μ were replaced by a weak band at 6.1μ and new bands at 13.5 and 13.7μ. Heating XXIII to 170° gave the alcohol (XXIV) which was hydrogenated and converted to the acetate (XXV). Pyrolysis of the acetate gave XXVI, whose structure, as well as those of XXIV and XXV, was assigned on the basis that it was different from that of longifolene. It had been hoped that the Diels-Alder step would have given alcohol XXVII which would have undergone the above series of reactions to give longifolene.

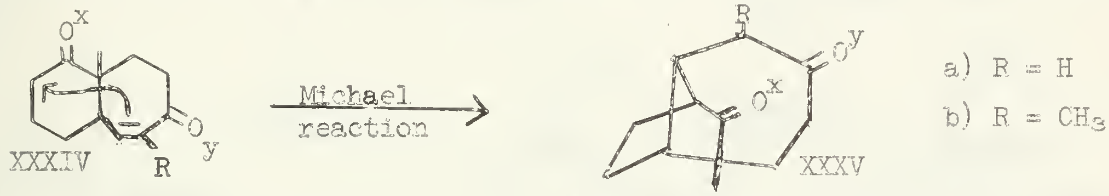
Cation-olefin addition and the Michael reaction were also considered. Early attempts by Scherrer[39] started with XXVIII. An attempted Michael reaction of XXVIII to give XXX, the fused-ring system of longicamphor, gave the tricyclic alcohol XXIX instead. Treatment of XXVIII with acid in order to obtain XXX also failed. The product obtained was not characterized.



An attempt to condense XXXI with the unsaturated nitrile (XXXII), utilizing potassium t-butoxide, sodium amide, triethylamine or tritylsodium as the base, to give structure XXXIII which would then undergo ring expansion to give the longicamphor ring system failed to give any adduct[39].



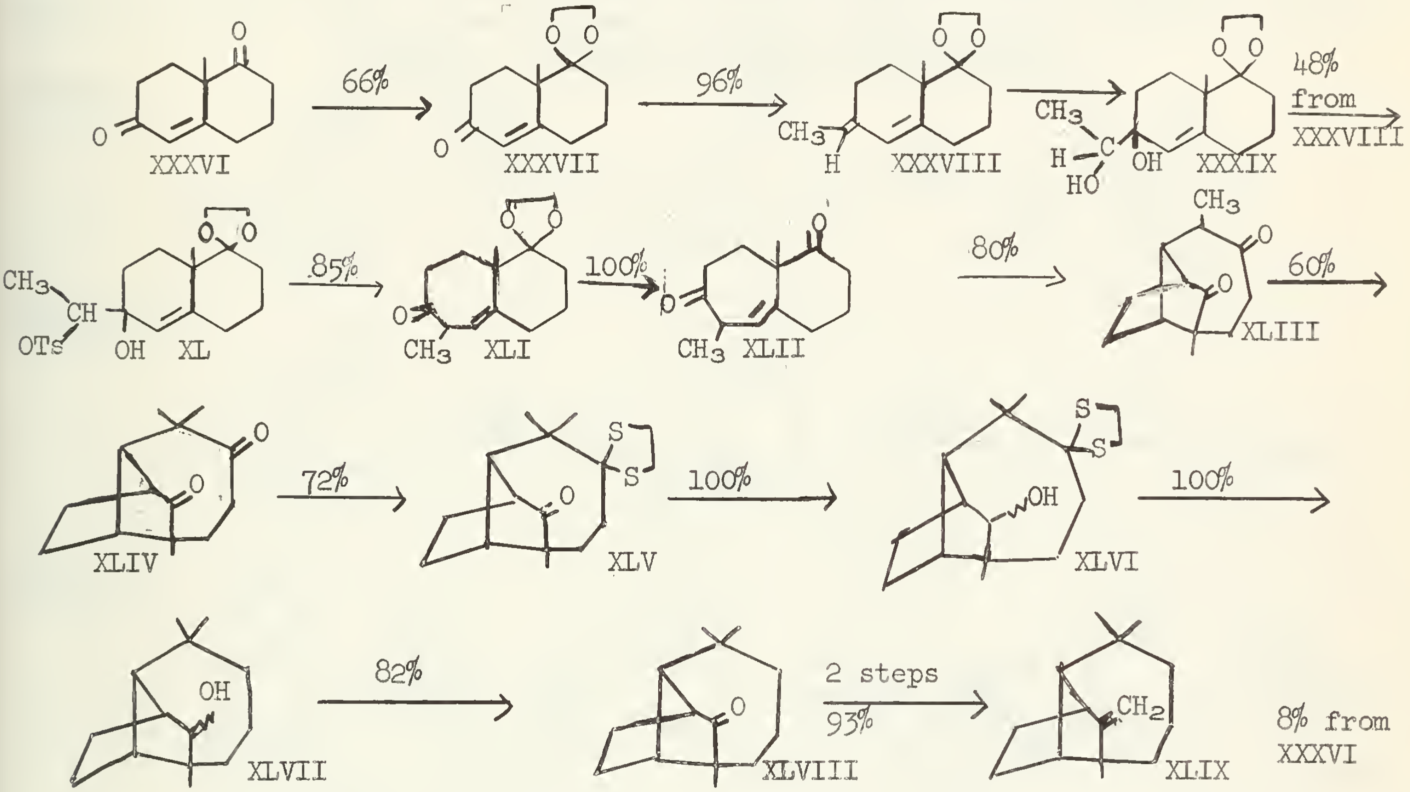
Corey and co-workers[44] decided to synthesize the bicyclic diketone (XXXIV) and perform ring closure via an internal Michael reaction[45,46] to give the tricyclic diketone (XXXV).



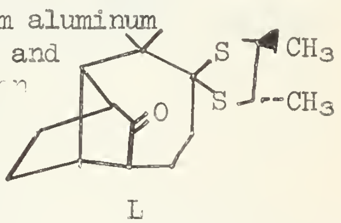
It was decided that the use of $R=CH_3$ would be more advantageous than R=H since the methylation step that would follow would be facilitated by the presence of one methyl group already in the position being methylated. The "y" carbonyl would be reduced to $-CH_2-$ and the "x" carbonyl converted to $>C=CH_2$. For their starting material Corey and co-workers used the Wieland-Miescher ketone (XXXVI)[47].The starting ketone was converted into the monoketal (XXXVII) with retention of the α,β-unsaturated carbonyl system and the ketal was converted to the ethylidine derivative (XXXVIII) via the Wittig reaction using dimethylsulfoxide anion as the base for the generation of the Wittig reagent[48]. The diene was selectively hydroxylated to the diol (XXXIX) using one equivalent of osmium tetroxide in ether-pyridine at 0° and utilizing the mild sodium bisulfate-pyridine isolation procedure. The diol was converted to the secondary p-toluenesulfonate derivative (XL). The solvolytic ring expansion of the p-toluenesulfonate had to be carried out under essentially nonacidic conditions due to the ketal function and the easily dehydrated tertiary alcohol. The reaction of XL at 50° in tetrahydrofuran containing lithium perchlorate (to facilitate ionization of the p-toluenesulfonate) and suspended calcium carbonate, to insure neutrality, gave a mixture of products from which the unsaturated cycloheptenone (XLI) was isolated. The structure of XLI was indicated by the presence of a band in the infrared due to an unconjugated carbonyl group (5.85μ) and the NMR spectrum (presence of peaks due to one vinyl proton, four ketal protons, one angular methyl group and one methyl group attached to -CH=). The isomerization of XLII to the conjugated diketone and subsequent internal Michael reaction proved to be more difficult than Corey had anticipated. Strong bases such as sodium methoxide and potassium t-butoxide led to degradation products of the desired tricyclic diketone (XLIII). Weaker bases were also without effect even at 100°. The internal Michael reaction was effected starting from XLI in ethylene glycol containing triethylamine at 225° for 24 hr. The methylation was effected by the tritylsodium-methyl iodide procedure[49] to give the desired product (XLIV). A single sharp peak in the NMR due to $>C(CH_3)_2$ at δ1.15 (6 protons) in addition to an angular methyl peak at δ 1.32 (3 protons) indicated that the methylation occurred in the desired position. The reduction of the desired carbonyl group was not effected by normal procedures. Direct Wolff-Kishner

reduction of XLIV did not give the desired product, longicamphenilone(XLVIII). The diketone(XLIV) was converted to the thioketal(XLV), but desulfurization with Raney nickel was unsuccessful. However, lithium aluminum hydride reduction of XLV to give the alcohol (XLVI) followed by direct Wolff-Kishner reduction by the method of Georgian, *et.al.*[50] afforded the desired product, *dl*-longicamphenilol(XLVII) which was oxidized with chromic acid to *dl*-longicamphenilone. Longicamphenilone was methylated with excess methyl lithium to give the tertiary alcohol which was dehydrated in cold pyridine using thionyl chloride to give *dl*-longifolene(XLIX). The synthetic scheme is outlined in figure 1.

FIGURE 1. TOTAL SYNTHESIS OF *dl*-LONGIFOLENE



Once the total synthesis was completed, Corey and co-workers decided to determine if the optically active product could be synthesized. This was accomplished starting with synthetic, racemic ketone(XLIV). This ketone was treated with L(+)-2,3-butanedithiol to give a mixture of diastereoisomeric thioketals from which the desired isomer (L) was isolated in pure form by chromatography. Reduction of L with lithium aluminum hydride, further reduction by the Georgian-Wolff-Kishner method[50] and subsequent oxidation with ruthenium tetroxide gave (+)-longicamphenilone identical with natural material by vapor phase chromatographic and infrared analyses. The conversion of (+)-longicamphenilone to (+)-longifolene was accomplished by the same method utilized in the total synthesis.

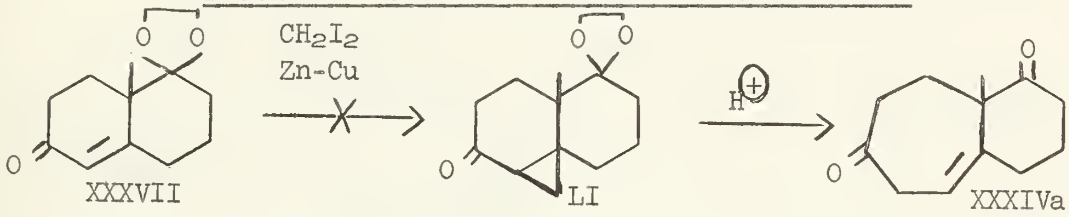

L

It might now be of some interest to consider the methods that were attempted in order to effect the ring expansion step[51]. Schemes A and B required the formation of a cyclopropane ring via the Simmons-Smith reagent and diazomethane respectively. Both schemes failed at the first step. Scheme C utilized the pyrrolidine enamine of XXXVII. Hydrochloric acid was added to the enamine to give LII. It was the author's intention to add potassium cyanide, oxidize the product to the amide and reduce the amide to the amine. Nitrous acid treatment of the amine would give the diazonium salt which would react, probably via a pinacol rearrangement, to give the enamine of the unconjugated cycloheptenone. However, the cyanide addition failed and direct diazomethane addition to LII was tried but also failed. The Reformatsky reaction (scheme E) of XXXVII with ethyl bromoacetate gave the α-hydroxy ester which was converted to the α-hydroxy acid (LIII). Kolbe electrolysis of the acid failed to give the desired XXXIVa as did treatment with lead tetraacetate (scheme F). Treatment of XXXVII with methylene triphenylphosphorane (scheme G) gave the diene LIV which was converted to the diol by treatment with osmium tetroxide. The tosylate was synthesized and solvolysis gave the aldehyde(LV) instead of ring expansion. In scheme H, LIV was treated with perbenzoic acid to give the epoxide which was allowed to react with ammonia in the presence of sodium amide to give the α-hydroxy amine. Treat-

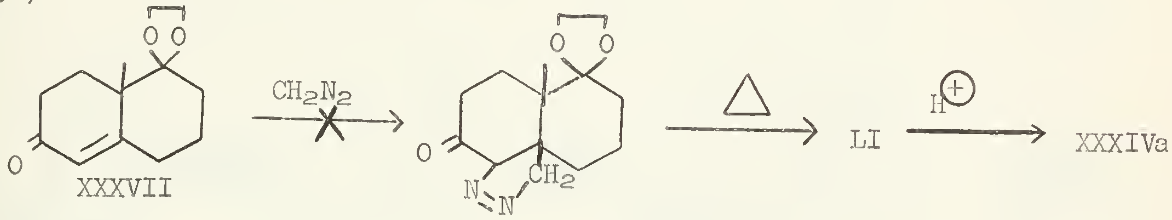
ment of the amine with nitrous acid gave the aldehyde(LV). In scheme I, LIV was treated with lead tetraacetate in an unsuccessful attempt to obtain the enol ester LVI. In scheme J, XXXVIII was hydrogenated to give the saturated ketone which was allowed to react with ethyl bromacetate and zinc to give the α-hydroxy ester(LVII). Dehydration of the ester with thionyl chloride gave LVIII. The diol(LIX) was obtained by treatment of LVIII with osmium tetroxide, and cleavage of the diol gave LX. An attempt to condense LX with base to give LXI was unsuccessful. Both schemes K and L were successful and differed only in that in K, diol XXXIX was treated with p-nitrobenzenesulfonyl chloride and gave an overall yield of 20% of XLI whereas scheme L, that outlined in the total synthesis, gave a 47% yield of XLI using p-toluenesulfonyl chloride. Schemes A-K are outlined in figure 2.

FIGURE 2. ATTEMPTS TO EFFECT RING EXPANSION

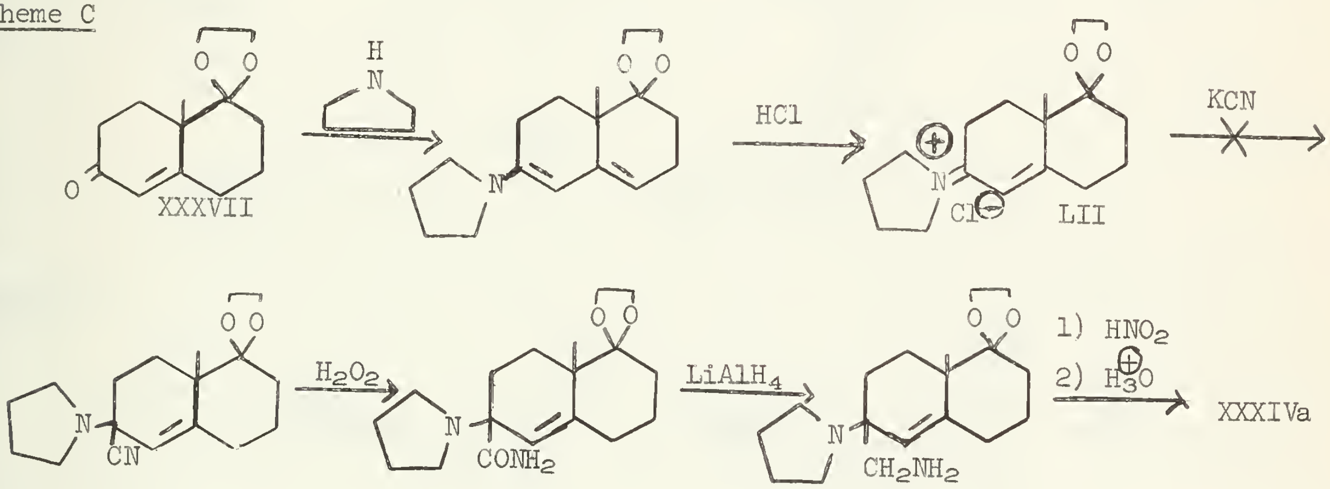
Scheme A


O O
O
XXXVII
CH_2I_2
Zn-Cu
O O
O
LI
$H^{\oplus}$
O
O
XXXIVa

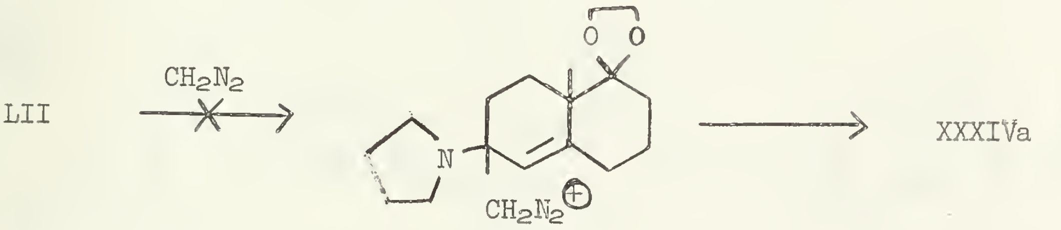
Scheme B (52)


O O
O
XXXVII
CH_2N_2
O O
O
N
N
CH_2
△
LI
$H^{\oplus}$
XXXIVa

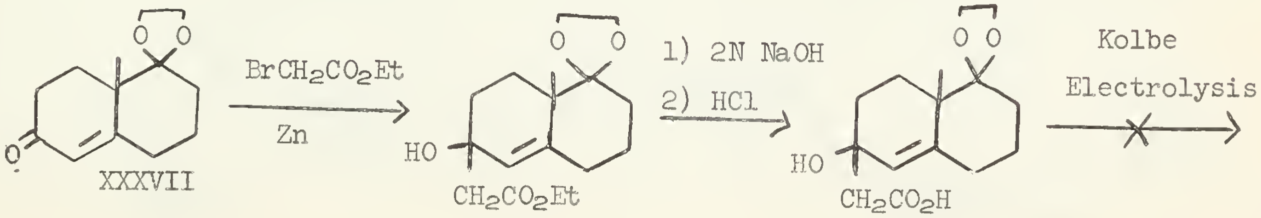
Scheme C

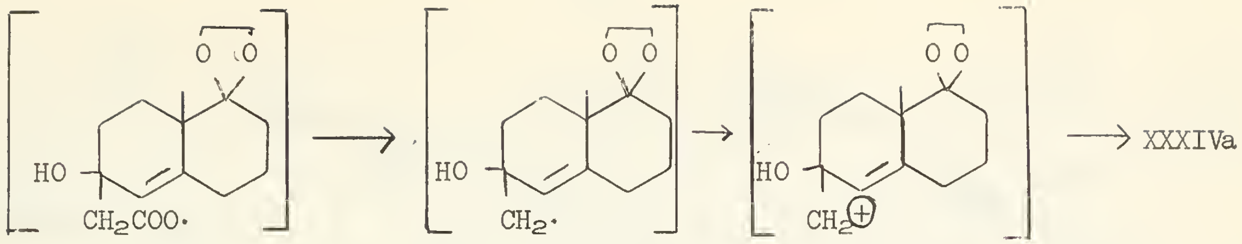

O O
O
XXXVII
H
N
O O
N
HCl
O O
N
Cl
LII
KCN
O O
N
CN
H_2O_2
O O
N
$CONH_2$
$LiAlH_4$
O O
N
CH_2NH_2
1) HNO_2
2) $H_3O^{\oplus}$
XXXIVa

Scheme D

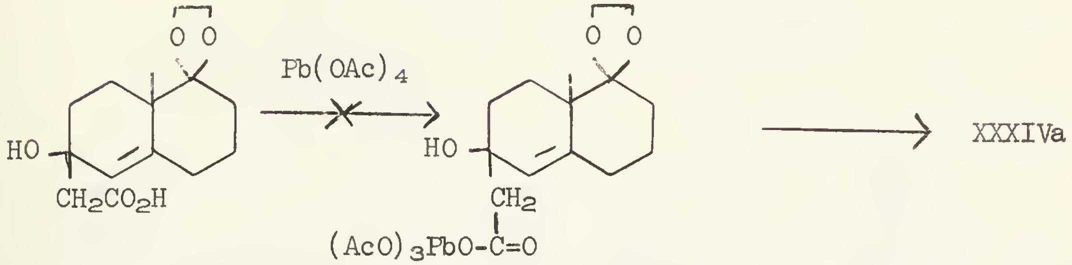

LII
CH_2N_2
O O
N
$CH_2N_2^{\oplus}$
XXXIVa

Scheme E

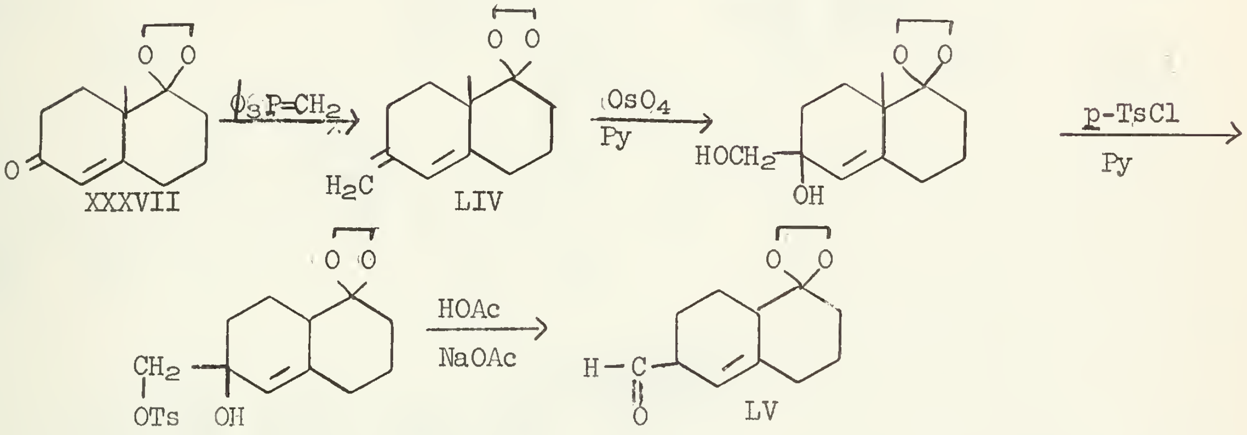

O O
O
XXXVII
$BrCH_2CO_2Et$
Zn
O O
HO
CH_2CO_2Et
1) 2N NaOH
2) HCl
O O
HO
CH_2CO_2H
Kolbe
Electrolysis


O O
HO
CH2COO·
O O
HO
CH2·
O O
HO
CH2⊕
XXXIVa

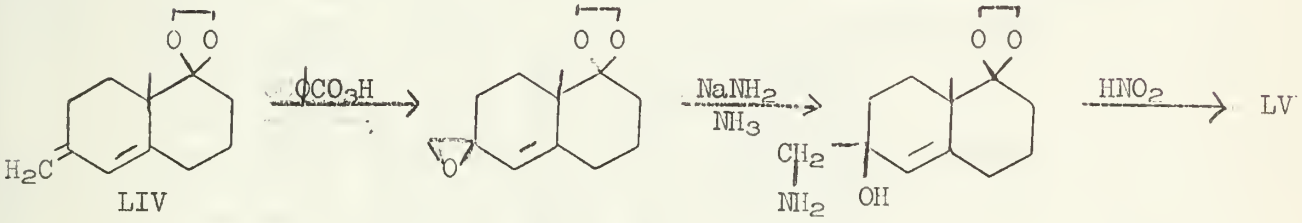
Scheme F


O O
HO
CH2CO2H
Pb(OAc)4
O O
HO
CH2
(AcO)3PbO-C=O
XXXIVa

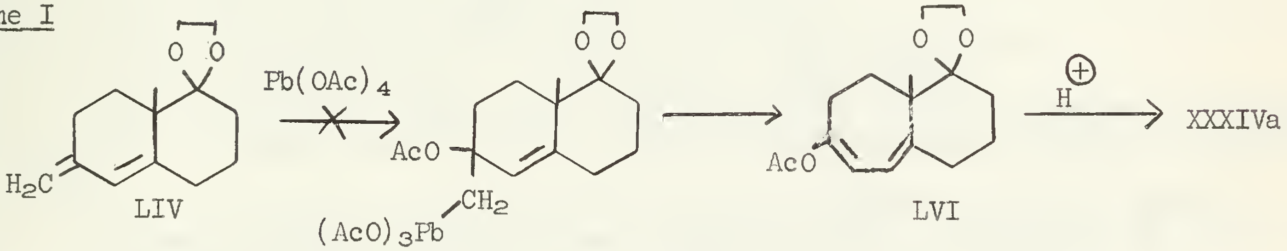
Scheme G


O O
O
XXXVII
φ3P=CH2
H2C
LIV
OsO4
Py
HOCH2
OH
p-TsCl
Py
CH2
OTs
OH
HOAc
NaOAc
H—C
O
LV

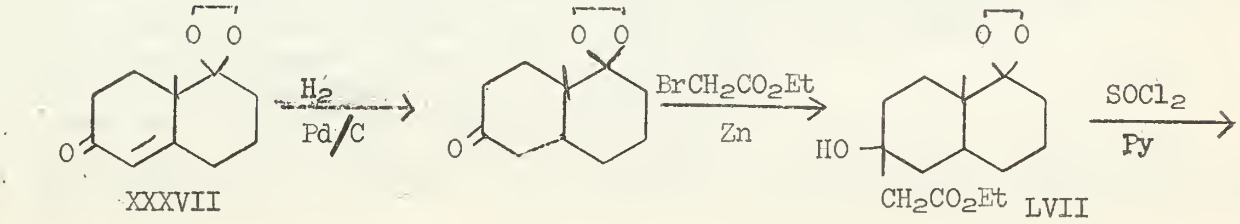
Scheme H

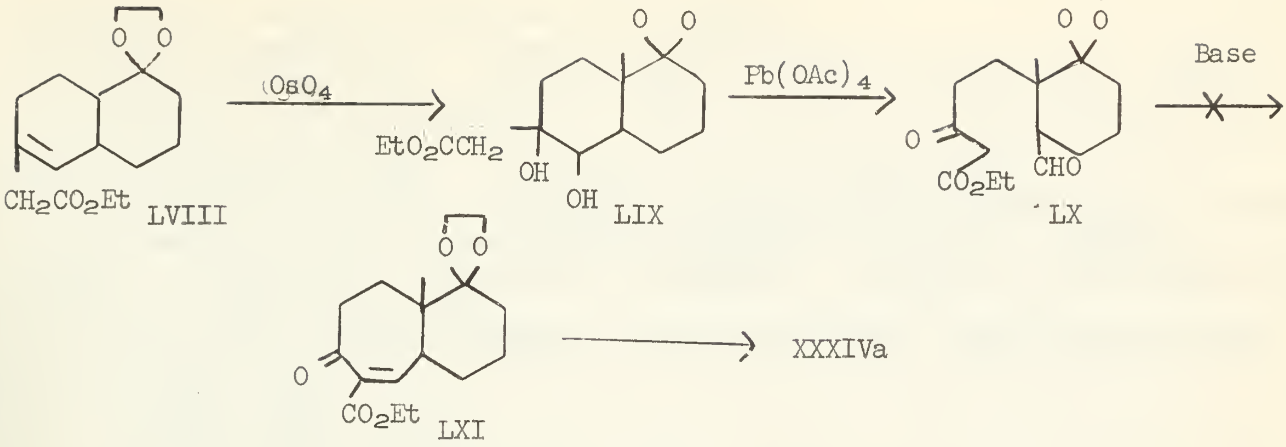

O O
H2C
LIV
φCO3H
O
NaNH2
NH3
CH2
NH2
OH
HNO2
LV

Scheme I

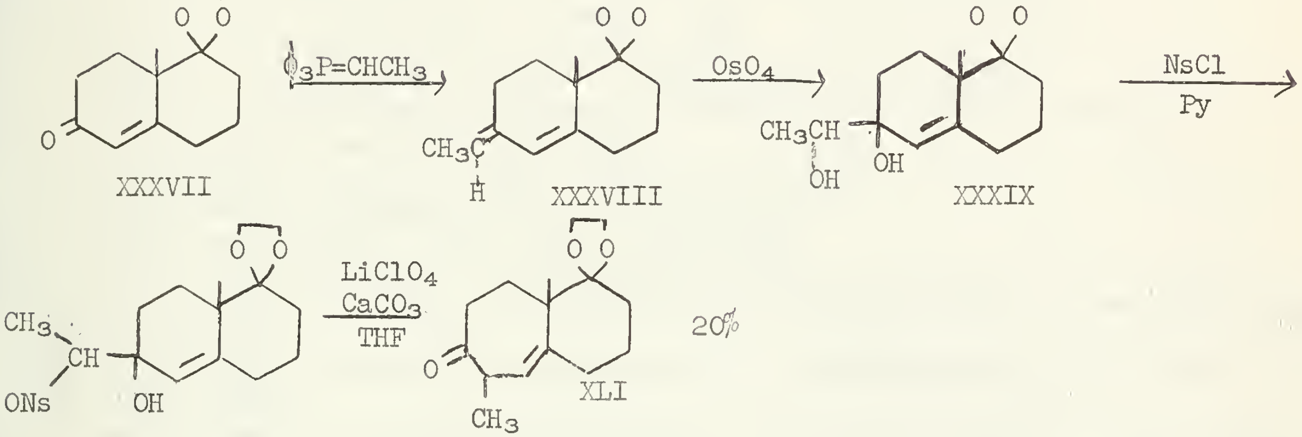

O O
H2C
LIV
Pb(OAc)4
AcO
CH2
(AcO)3Pb
AcO
LVI
H⊕
XXXIVa

Scheme J


O O
O
XXXVII
H2
Pd/C
O
BrCH2CO2Et
Zn
HO
CH2CO2Et
LVII
SOCl2
Py


OsO$_4$
Pb(OAc)$_4$
Base
EtO$_2$CCH$_2$
OH
OH
CH$_2$CO$_2$Et
LVIII
LIX
CO$_2$Et
CHO
LX
CO$_2$Et
LXI
XXXIVa

Scheme K


ϕ_3P=CHCH$_3$
OsO$_4$
NsCl
Py
XXXVII
CH$_3$C
H
XXXVIII
CH$_3$CH
OH
OH
XXXIX
CH$_3$
CH
ONs
OH
LiClO$_4$
CaCO$_3$
THF
CH$_3$
XLI
20%

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HOMOGENEOUS CATALYTIC HYDROGENATION

Reported by Robert Y. Ning November 23, 1964

Introduction: Three types of homogeneously catalysed reactions of molecular hydrogen have been observed.

1. Exchange with deuterium or with protolytic substances:

$$H_2 + D_2 \longrightarrow 2HD$$
$$H_2 + D_2O \longrightarrow HD + HDO$$

2. Reduction of substances which are also reduced readily by "reversible" electron-donors or at electrodes:

$$2Ag^+ + H_2 \longrightarrow 2\,Ag(s) + 2H^+$$
$$\text{Quinone} + H_2 \longrightarrow \text{Hydroquinone}$$

3. Reactions with other "inert" molecules, particularly reactions in which new carbon-hydrogen bonds are formed:

$$R_2C = CR_2 + H_2 \longrightarrow R_2CHCHR_2$$
$$R_2C = NH + H_2 \longrightarrow R_2CHNH_2$$

Extensive qualitative and kinetic data for the first two types of reactions are summarized in several reviews (2,3,4). Homogeneous catalysis of the third type of hydrogenation, excluding biological systems, was almost unknown in 1959 - the year of a review by Halpern (4), except for one notable case - that of dicobalt octacarbonyl. Significant amounts of competing hydrogenation have been noticed in hydroformylation (oxo) processes in which mixtures of hydrogen and carbon monoxide are used over cobalt catalysts. Dicobalt octacarbonyl formed in solutions has been implicated as the active hydrogenation catalyst. The oxo process has been studied extensively, and data on dicobalt octacarbonyl and other cobalt carbonyls can be found in several reviews (1,4, 34, 35, 37), to which may be added a recent reference (36). This seminar will present data on new homogeneous catalytic systems for hydrogenation reactions of type 3.

Platinum Complexes: Flynn and Hulburt (5) showed that when toluene or acetone solutions of ethyleneplatinous chloride are reacted with hydrogen at temperatures below -10°, in the presence of excess of ethylene bubbling through the catalyst solution, ethane may be formed without accompanying deposition of platinum. The reaction under these conditions appeared to be homogeneous, and the following mechanism has been proposed:

$$(PtCl_2C_2H_4)_2 + 2C_2H_4 \rightleftharpoons 2PtCl_2(C_2H_4)_2 \qquad (1)$$
$$2PtCl_2(C_2H_4)_2 + 2H_2 \longrightarrow (PtCl_2C_2H_4) + 2C_2H_6 \qquad (2)$$

Later (6), it was found that chloroplatinic acid in the presence of fivefold or more molar excess of stannous chloride can reduce ethylene rapidly and quantitatively to ethane at 25° and 1 atmosphere pressure. Similarly, acetylene was reduced to a mixture of ethane and ethylene. The exact nature of the active Sn-Pt complex in this system is uncertain. Pertinent to the catalytic activity of the complex is the ability of stannous chloride to promote the co-ordination of ethylene to platinum. Thus, reaction of ethylene at atmospheric pressure with a solution of K_2PtCl_4 containing stannous chloride gave a quantitative conversion to Zeise's salt, $KPtCl_3C_2H_4 \cdot H_2O$, within 1.5 hrs, while in the absence of stannous chloride, no Zeise's salt formed in 16 hrs. Furthermore, solutions of stannous chloride and chloroplatinic acid (6:1) in CH_3OD containing an excess of ethylene show a single n.m.r. absorption attributable to ethylene protons, shifted appreciably downfield compared to the absorption for ethylene in CH_3OD. This suggests an extremely rapid exchange between co-ordinated and free ethylene in the platinum-tin system.

Cr^{III}, Mn^{II}, Ni^{II}, Fe^{III}, Ru^{II}, Pd^{II}, Rh^{III}: Tulupov (7,8,9,10) reported the facile hydrogenation of cyclohexene catalysed by Cr^{III}, Mn^{II}, Ni^{II}, Fe^{III}. These cations are solubilized towards organic solvents as stearates. The isolation of an unstable ferric-cyclohexene complex was described, having the formula $[Fe(C_6H_{10})_4](O_2CC_{17}H_{35})_3$ and absorption maximum at 420 mμ. This was presented as a support for

the concept of activation of olefins towards hydrogenation via loose complex formation with metal ions. Recently Castro and Stephens (27) reported the homogeneous reduction of acetylenes by chromous sulfate in water or aqueous dimethylformamide at room temperature to give trans-olefins in high yields. Here, chromous sulfate was the reagent itself, and no hydrogen was used. The data are in accord with a rate-determining attack of Cr^{+2} upon a 1:1 acetylene-Cr^{+2} complex, the hydrogens transferred coming from two water molecules in the co-ordination spheres. Similar reductions of double bonds conjugated with carbonyl groups have been studied earlier by Kopple (33). Whether chromous ions can act in catalytic amounts in the presence of molecular hydrogen, and whether they are involved in the catalytic activities of Cr(III) in aqueous systems remains to be investigated.

Maleic, fumaric and acrylic acids were successfully reduced using chlororuthenate (II) complex as catalyst (11). The typical medium containing the catalyst for hydrogenation in this case was generated by reduction of $(NH_4)_2RuCl_6$ with $TiCl_3$ in aqueous 3 M HCl solution. Maleic acid in excess over Ru(II) was hydrogenated at conveniently measurable rates to succinic acid, over a temperature range from 70° to 90°, and following the reaction rate law $k(H_2)(Ru^{II})_{total}$, with $\Delta H^{\ddagger} = 19$ Kcal/mole, $\Delta S^{\ddagger} = -2$ e.u. The formation of a 1:1 complex of maleic acid with Ru(II) was detected spectrophotometrically, and a stability constant in 3 M HCl at 20° was found to be 5×10^3. The concentration of maleic acid and Ru(II) used in the kinetic runs were such that essentially all the Ru(II) ions were complexed. Based upon these findings, the following mechanism was proposed:

$$Ru^{II} + \text{Olefin} \longrightarrow Ru^{II}\cdot\text{Olefin (fast)} \quad \cdots \quad (3)$$

$$Ru^{II}\cdot\text{Olefin} + H_2 \xrightarrow{k} Ru^{II} + \text{saturated product} \quad \ldots \quad (4)$$

Ethanolic solutions of ethyl crotonate ($CH_3CH = CHCOOC_2H_5$) were found to take up hydrogen rapidly when a few drops of 1% solution of $PdCl_2$ was added to them (12). Numerous ions of both transition and non-transition metals were found to be promoters in this system when added in trace amounts. With the most active, Na^+, the activity was as much as 7 times that of $PdCl_2$ alone. There is reason to doubt, however, whether hydrogenation in these solutions occurred entirely homogeneously. Grey spongy metallic palladium separated from the initially clear amber solutions as the reactions proceeded. The fact that the rate of uptake of hydrogen actually dropped as more palladium precipitated was taken by the authors to indicate that the palladium precipitated was catalytically inactive and that hydrogenation was truly homogeneous.

Complexes of rhodium(III) have recently been shown to catalyse hydrogenation of hexenes (38). Isomerization of cis-hex-2-ene to trans-hex-2-ene was reported to occur prior to reduction. Double bond migrations, which are recognized as complications in homogeneous catalytic systems, are being investigated by Harrod and co-workers (39).

Alkoxide Ions: Under drastic conditions, typically 130 atmospheres hydrogen, 200° and 25 hours, benzophenone can be reduced to benzhydrol in a homogeneous solution with 1 M t-BuOK in t-BuOH (13). Equilibria of type (5) leading to the exchange of D_2 with water in the presence of ^-OH, and with NH_3 in the presence of $^-NH_2$ are well documented (4,14,15). It seems likely that reduction of benzophenone involves the generation of hydride ion by strongly basic t-butoxide ion, followed by nucleophilic attack by hydride on a suitably polarized double bond as shown by equations 6-8. The drastic

$$H_2 + OH^- \rightleftharpoons H^- + H_2O \qquad (5)$$

$$RO^- + H_2 \rightleftharpoons ROH + H^- \qquad (6)$$

$$H^- + R_2C = O \rightleftharpoons R_2CH\text{-}O^- \qquad (7)$$

$$R_2CH\text{-}O^- + ROH \rightleftharpoons R_2CHOH + RO^- \qquad (8)$$

conditions severely limit the utility of this catalytic system. Cyclohexene was not reduced under these conditions.

Boron Alkyls (R_3B): The addition of borohydrides to olefins is a general and favorable reaction (16). The uncatalyzed hydrogenolysis of carbon-boron bonds in alkyl boranes to form borohydrides and alkanes have also been reported (17,18). These observations indicate that boranes might be effective homogeneous catalysts for the hydro-

genation of olefins according to the following scheme (9-11):

$$BR_3 + H_2 \longrightarrow R_2BH + RH \tag{9}$$

$$R_2BH + R'CH = CH_2 \longrightarrow R'CH_2CH_2BR_2 \tag{10}$$

$$R'CH_2CH_2BR_2 + 3H_2 \longrightarrow R'CH_2CH_3 + 2RH + BH_3 \tag{11}$$

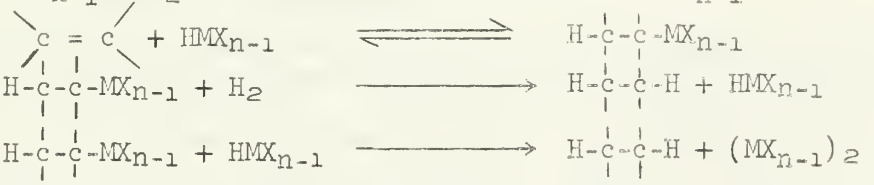
Indeed preliminary success was reported by DeWitt, Ramp and Trapasso (19). These workers reported quantitative reduction of cyclohexene and caprylene, containing 3.8 mole % tri-n-butylborane, in three hours at 220° under 1000 psi hydrogen. The reaction rate is highly temperature dependent; essentially no reaction occurred below 200°. The high temperature required has been identified with the hydrogenolysis of the carbon-boron bond. The reduction of double bonds in high polymers, normally a difficult task with heterogeneous catalysts, was achieved with boranes. Polybutadiene gave a crystalline polymer with infrared spectra and melting characteristics similar to those of polyethylene, while polyisoprene similarly reduced gave spectra essentially identical with that of the random copolymer of ethylene and propylene.

Koster, Gunter and Paul have shown that the hydrogenolysis of boron-carbon bonds is facilitated by the presence of tertiary aliphatic amines (18).

Soluble Ziegler Type Catalysts: Sloan, Matlack and Breslow reported effective hydrogenation of olefins using bis(cyclopentadienyl)-titanium dichloride-triethylaluminum or triisobutylaluminum-tetraisopropyl titanate, soluble Ziegler catalysts of the type used in the polymerization of ethylene (20). They found that Co(II and III), Cr(III), Fe(III), Mn (II and III), Mo(VI), Ni(II), Pd(II), Ru(III), V(V) and Zr(IV) as acetylacetonates or alkoxides are generally effective towards olefins when used with 1/3 to 1/10 as much of trialkylaluminum. The most active catalysts appeared to be Co(III), Fe(III) and Cr(III) acetylacetonates combined with triisobutylaluminum. Toluene or n-heptane were used as solvents. Catalyst levels of 2-4 mole % transition metal based on the olefin were employed, under mild conditions of 3.7 atmospheres hydrogen and 30-50°. For each catalyst tested, one or more of the following olefins were reduced: cyclohexene, 1-octene, 2-methyl-2-butene, 2-pentene, tetramethylethylene and stilbene. Tetramethylethylene was the most difficult of these olefins to reduce, 75% hydrogenation having been achieved in 18 hrs. It should be noted, however, that these catalysts failed with a variety of other substrates including ketones, aldehydes, nitriles, nitro-compounds, azo-compounds and esters. A postulated mechanism for hydrogenation in these systems must be speculative, since the structures of the catalysts are unknown. Sloan and co-workers proposed the following scheme as being likely (12-18):

$$R_3Al + MX_n \longrightarrow R_2AlX + RMX_{n-1} \tag{12}$$

$$RMX_{n-1} + H_2 \longrightarrow RH + HMX_{n-1} \tag{13}$$



$$>C=C< + HMX_{n-1} \rightleftharpoons H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-MX_{n-1} \tag{14}$$

$$H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-MX_{n-1} + H_2 \longrightarrow H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-H + HMX_{n-1} \tag{15}$$

$$H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-MX_{n-1} + HMX_{n-1} \longrightarrow H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-H + (MX_{n-1})_2 \tag{16}$$

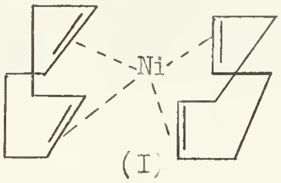
$$(MX_{n-1})_2 + H_2 \longrightarrow 2HMX_{n-1} \tag{17}$$

$$RCH_2CH_2MX_{n-1} \longrightarrow HMX_{n-1} + RCH = CH_2 \tag{18}$$

These workers cited the alkylation of bis(cyclopentadienyl)-titanium dichloride by triethylaluminum postulated by Breslow and Newburg (21) as support for reaction (12). It was not pointed out, however, that in the case cited, alkylation resulted only when the triethylaluminum-titanium ratio was greater than one; in the case at hand, triethylaluminum was used in much smaller amounts. The postulation of addition of transition metal hydrides to carbon-carbon double bonds is well precedented (4,22). The over-all scheme was admitted to be highly simplified. Likely occurrences such as the co-ordination of olefins to metal ions or metal hydrides were omitted. The possibility of involvement of aluminum in these systems remains in the mind of this reviewer, in view of the established reversible addition of aluminum hydrides to olefin (23), and

the ease in the cleavage of aluminum-carbon bonds by compounds containing active hydrogen (24).

Mixing triethylaluminum with Ni(II) carboxylates, Lapporte and Schentt (25) obtained a catalyst which they found to be effective towards the reduction of aromatic rings. When triethylaluminum is added to a solution of Ni(II) 2-ethylhexanoate in heptane or benzene, an exothermic reaction occurs giving off a gaseous mixture, which contains greater than 95% ethane. A black solution remained containing the active catalyst of unknown structure. The ultimate amount of gas evolved and the highest catalytic activity concurred at aluminum-nickel ratios of 3-4 : 1. The black catalyst solution is not separated by ultracentrifugation, and is neither pyrophoric nor paramagnetic. This led to speculation that zero-valent nickel solubilized by π-complex with organic ligands might have been formed. Wilke and co-workers had shown earlier (26) that bis-1,5-cyclooctadiene nickel (0) (structure I), a crystalline complex, could be isolated from reaction of trialkylaluminum with nickel acetylacetonate in presence of 1,5-cyclooctadiene.



(I)

Pentacyanocobaltate(II): A mixture of aqueous solutions containing five or more moles of KCN to every mole of cobalt(II) chloride gives a catalytic solution which rapidly absorbs approximately 0.7 atom of hydrogen per cobalt atom. This phenomenon was first noticed by Iguchi in 1942 (28), but catalytic hydrogenation of organic substrates by this system was discovered only recently (22,29). At room temperature and one atmosphere pressure, Kwiatek, Mador and Seyler (22) found that conjugated olefins absorbed one mole equivalent of hydrogen to yield mono-olefins exclusively. The resulting mono-olefins are largely trans, resulting from 1,4-addition of hydrogen. Mono-olefins and non-conjugated dienes are not reduced. Activities toward double bonds conjugated with phenyl rings and carbonyl of aldehyde and carboxyl functions are erratic. The following mechanism for the reduction of butadiene has been proposed by Kwiatek and co-workers:

$$2[\mathrm{Co^{II}(CN)_5}]^{3-} + \mathrm{H{:}H} \rightleftharpoons 2[\mathrm{Co^{III}(CN)_5{:}H}]^{3-} \tag{19}$$

$$[\mathrm{Co(CN)_5{:}H}]^{3-} + \mathrm{C_4H_6} \rightleftharpoons [\mathrm{Co(CN)_5(C_4H_7)}]^{3-} \tag{20}$$

$$[\mathrm{Co(CN)(C_4H_7)}]^{3-} + [\mathrm{Co(CN)_5{:}H}]^{3-} \longrightarrow 2[\mathrm{Co(CN)_5}]^{3-} + \mathrm{C_4H_8} \tag{21}$$

$$\Big\downarrow \mathrm{HOH}\ \ ?$$

$$\mathrm{C_4H_8} + [\mathrm{Co(CN)_5OH}]^{3-}$$

Adamson (40) showed that the cobalt(II) cyanide complex in aqueous solutions containing cobaltous ion and five or more equivalents of cyanide ions is pentacyanocobaltate(II) anion (formula II). Evidences were elemental analysis of the isolated potassium salt and titrimetric determinations of the equivalent weight of the salt and bound cyanide per mole cobalt in solution. King and Winfield (41) characterized pentacyanocobaltate(II) ion by ultraviolet spectrum, which consists of six bands between 200-1000 mμ. They found that by forming the complex using methanol or dimethylsulfoxide as solvents, similar spectra were obtained, with minor shifts of the peaks. When an aqueous solution of pentacyanocobaltate(II) ion absorbs hydrogen, the ultraviolet spectrum collapses towards a single maximum at 305 mμ. The same band at 305 mμ was generated by treating the aqueous solution of pentacyanocobaltate(II) with sodium borohydride. These workers attributed the new band to the formation of a

$$[\mathrm{Co^{II}(CN)_5}]^{-3} \qquad\qquad [\mathrm{Co^{III}(CN)_5{:}H}]^{-3} \longleftrightarrow [\mathrm{Co^{II}(CN)_5{\cdot}H}]^{-3} \longleftrightarrow [\mathrm{Co^{I}(CN)_5H}]^{-3}$$

(II) (III)

hydrido complex of structure III, arising possibly from reactions 22 and 23. Structure III can be represented by any of the three resonance forms. Griffith and Wilkinson (42)

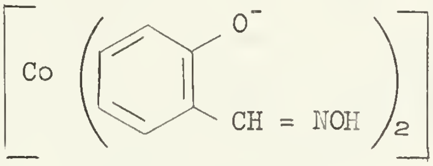
$$[Co^{II}(CN)_5]^{-3} + H_2 \underset{}{\overset{slow}{\rightleftharpoons}} [H_2Co(CN)_5]^{-3} \qquad (22)$$

$$[H_2Co(CN)_5]^{-3} + [Co^{II}(CN)_5]^{-3} \rightleftharpoons 2\ [HCo^{III}(CN)_5]^{-3} \qquad (23)$$

in a nuclear magnetic resonance study, found that III in aqueous solution gives a proton signal at 17.4 p.p.m. on the high field side of the reference protons in water, quite in agreement with the known values of 14-22 p.p.m. shown by hydrogens bonded to transition metals (43).

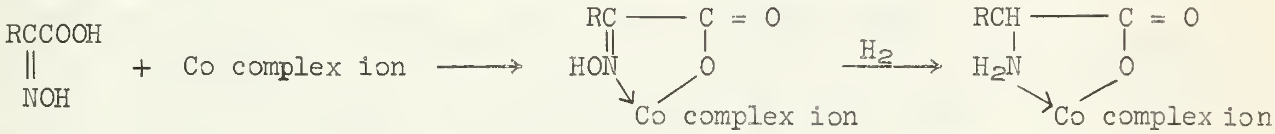
The hydrogenation of sodium sorbate ($CH_3CH = CH\text{-}CH = CHCOO^-Na^+$) with a pentacyanocobaltate(II) posed an interesting test case in which there are three double bonds in conjugation. Mabrouk and co-workers (32) obtained 2-, 3- and 4-hexenoates in 82, 17 and 1% yields respectively using water as solvent. When methanolic solution was used however, 2-hexenoate was obtained in 96% yield.

Murakami and co-workers successfully hydrogenated unsaturated organic ligands complexed with Co(II) and Co(III) in homogeneous aqueous solutions (30,31). Complex IV, for instance, was hydrogenated at 50°, 100 atmospheres of hydrogen, for 70 hrs. to give ortho-hydroxybenzylamine in 47% yield. Addition of 5-6 moles of KCN per mole cobalt to these solutions was found to greatly enhance the ease of hydrogenation.



(IV)

It is interesting to note that the best yields were obtained when organic ligands were added to preformed solutions containing an equivalent amount of Co(II) complexed with 5 moles of cyanide (44). Numerous oximes and imides of α-ketocarboxylic acids were hydrogenated to the corresponding amino acids in 8 hrs, at 40-70° and 100 atmospheres hydrogen. Murakami and co-workers feel that the substrates are powerful enough ligands to compete with cyanide ions for co-ordination with cobalt, and that reductions probably follow the path shown. The number of cyanide ions co-ordinated to Co in the intermediate is not known.



Remark in summary: A general explanation for the role played by most catalysts in these systems has been offered by Halpern (4) in terms of schematic orbital splitting diagrams (figure 1). The closed-shell electron configuration of the hydrogen molecule

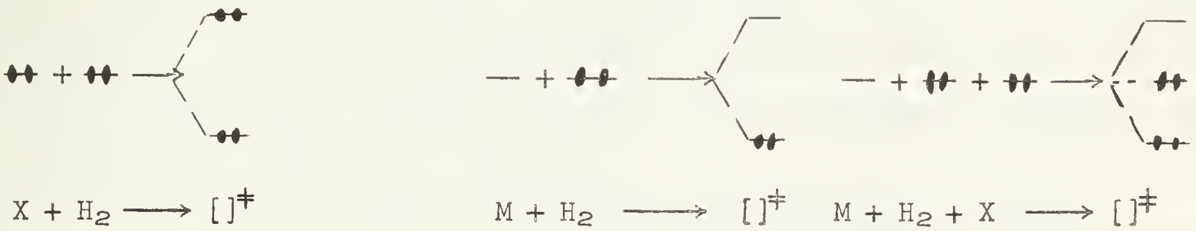


Figure 1

produces strong repulsion forces when it approaches to within reacting distance of another electronically-saturated molecule (one in which the low-lying orbitals are filled). The activated complex in such a reaction generally contains more electrons than can be accommodated in low-energy orbitals; this is reflected in high activation energy. Little electronic promotion will be required, however, if the reactant is a

species (M) having an empty orbital of sufficiently low energy (see figure). Such a species can also act as a catalyst for the direct reaction of two electronically-saturated molecules by providing an orbital to accept "unwanted" electrons and thus lowering the energy of the activated complex.

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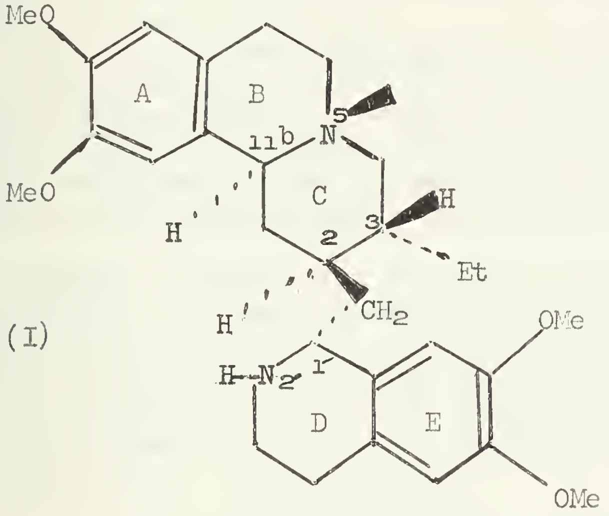
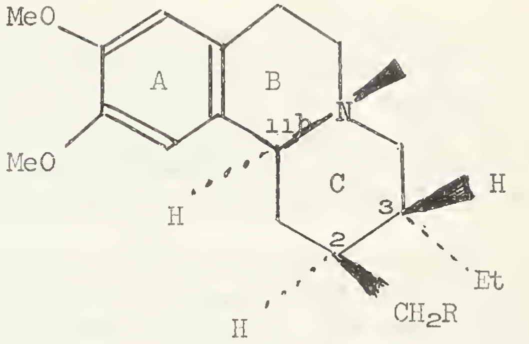
TOTAL SYNTHESIS OF (-)-EMETINE

Reported by R. Lambert November 30, 1964

Emetine (I), isolated from the tropical plant Ipecacuanha, is the most active of related isoquinoline derived alkaloids for the treatment of amoebic dysentery. The correct structure (I) suggested by Robinson[1] and Battersby[2] on biogenetic grounds was confirmed independently by Battersby and Openshaw, and Pailar. A review of this structural work including the first laboratory synthesis of emetine by Preobrazhensky and Evstigneeva has appeared.[3] The relative and absolute orientations of emetine's (I) four asymmetric centers have been established largely by the work of Battersby[4,5,6,7,8,9] and van Tamelen.[10,11,12] Interestingly, the absolute configuration at position 2 of emetine (I) is the same as that at the corresponding carbon atom in those indole alkaloids thought to be biosynthesized from tryptophan, phenylalanine or their equivalents.[1,13]



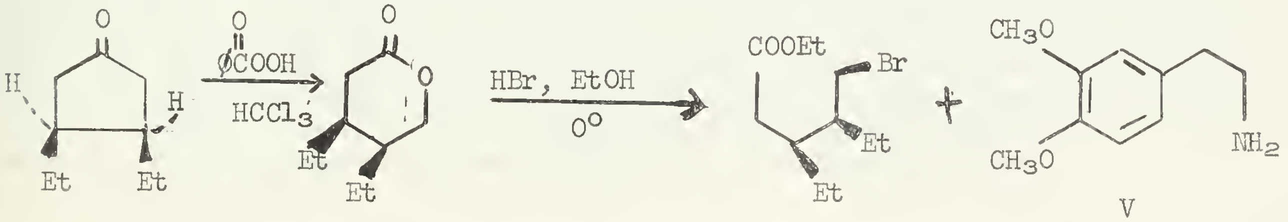
(I)



(II)

This seminar deals with the various procedures utilized in fabricating the general emetine skeleton with special emphasis on the stereospecificity of the individual approaches.

One of the major goals in the syntheses to be discussed has been establishing the necessary trans-configuration at the 2,3-position of emetine (I). That a trans-2,3-configuration is representative of the natural alkaloid was shown by the following synthetic conversions. Battersby and coworkers[5,6] effected a Wolff-Kishner reduction on protemetine (II, R = CHO), known from previous work[7,8] to be stereochemically related to emetine, producing deoxyprotoemetine (II, R = CH_3). Natural emetine was recovered unchanged when subjected to the same treatment. Then by an unequivocal synthetic route from ethyl erythro- and threo-dl-3,4-diethyl-5-bromovalerate they fabricated the cis-2,3-and trans-2,3-diethyl bases (III)*, respectively. The synthetic route employed is illustrated using cis-3,4-diethylcyclopentanone whose stereochemistry was established by Koelsch and Stratton.[14] Each of the isomers III was cyclized with phosphoryl chloride to the benzoquinolizinium halide (IV) which on reduction gave product corresponding to alpha addition of hydrogen to C-11b of II (R=CH_3). Comparison of the solution infrared spectra of the cis- and trans-2,3-isomers (II, R=CH_3) thus obtained with material derived from protoemetine showed only the trans-2,3-isomer (II, R=CH_3)* to be identical. The synthetic material was not resolved.



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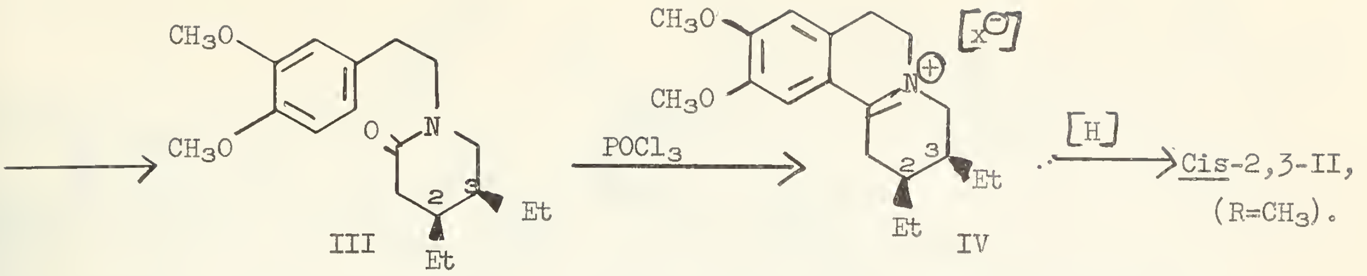
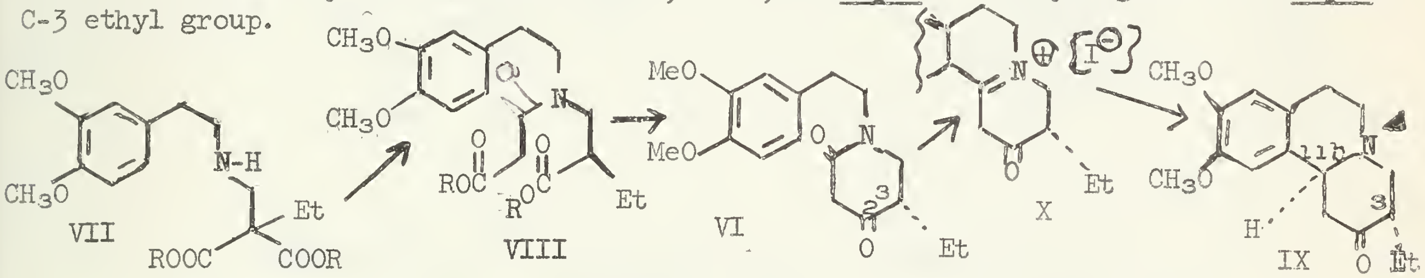
* Here and elsewhere in the abstract when optical isomerism is possible only one enantiomorph is shown.



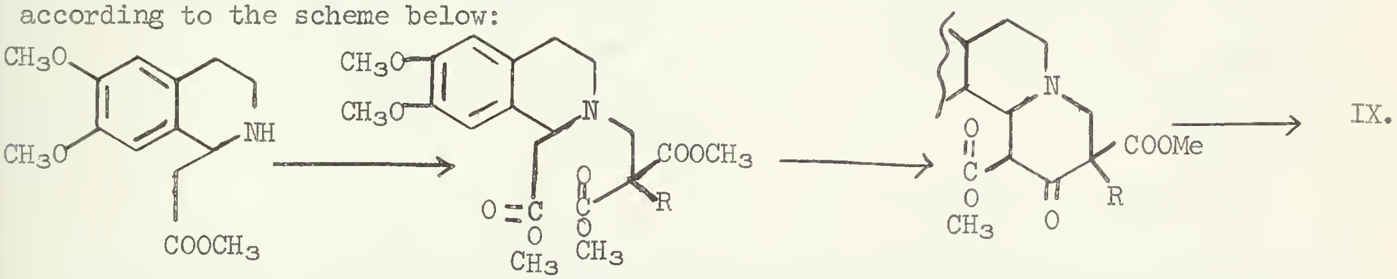
E.E. van Tamelen and coworkers[10,11,12] also synthesized the trans-2,3-lactam (III) employing ethyl dl-threo-3,4-diethyl-5-bromovalerate which had previously been used in another connection.[15] These authors compared trans-2,3-III with an intermediate (XVI) which they synthesized by a modified procedure initially employed by Preobrazhensky and Evstigneeva in their synthesis of emetine.[3] By stereospecifically converting XVI to trans-2,3-III they firmly established the trans-2,3 configurational requirement for natural emetine derivatives.

A most convenient starting point in several syntheses has been construction of a key intermediate such as VI. The first synthesis of VI was published by Ban[16] and with slight modification has been used by Osbond[17] and Battersby[18] in their syntheses. A Mannich condensation between homoveratrylamine (V), formaldehyde, and a substituted malonic acid gave the Mannich base (VII), which was decarboxylated, re-esterified, and treated with ethoxycarbonylacetyl chloride to yield VIII. Dieckmann cyclization gave VI.

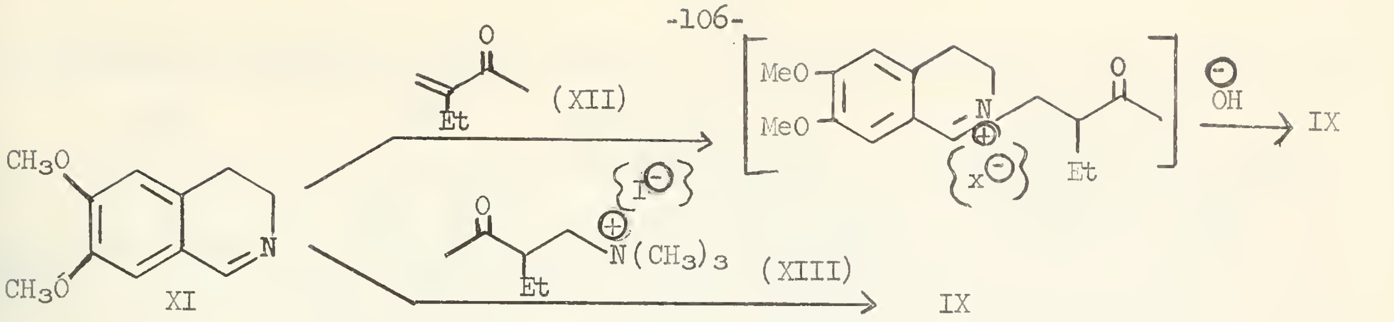
Recently, Osbond[19] has reported the conversion of VI into another popular intermediate IX, via a Bischler-Napieralski cyclization of the ketal of VI using phosphorus oxychloride in toluene followed by acid hydrolysis and addition of potassium iodide to give X in 73% yield. Reduction of X with potassium borohydride in methanol gave IX (94%). It should be noted that the most stable configuration of IX possesses the correct stereochemistry for natural emetine, i.e., an alpha C-11b hydrogen and an alpha C-3 ethyl group.



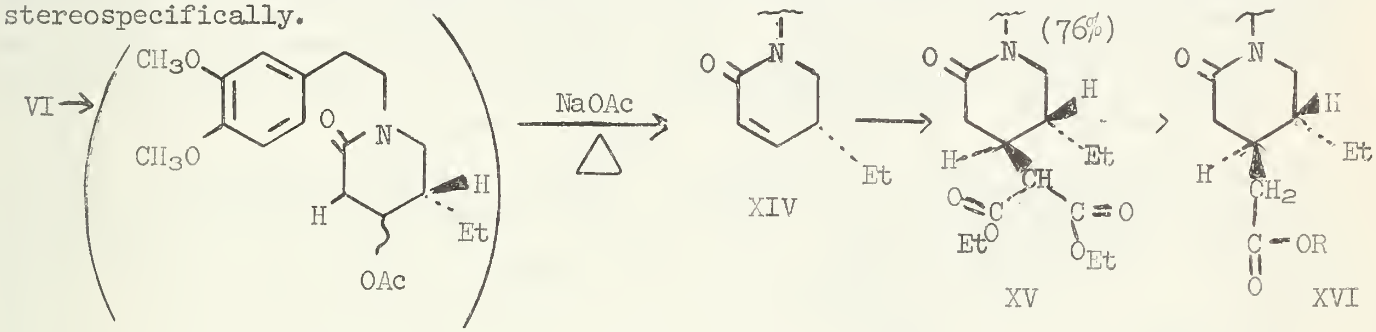
There have been numerous syntheses of IX, the first practical one being that of Battersby and coworkers[20]. Later, Brossi and coworkers[21] generalized this procedure according to the scheme below:

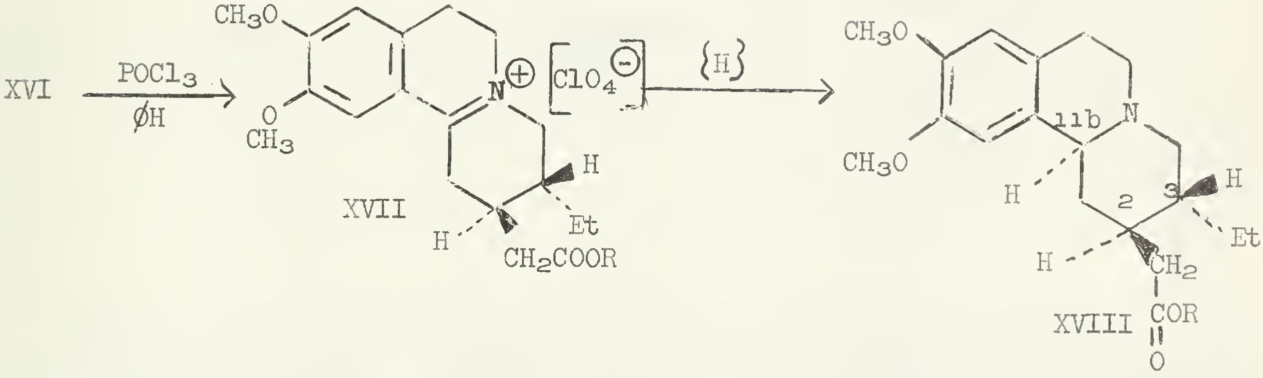


In 1960, as an outgrowth of degradative studies, Brossi and coworkers[22] showed that IX could be synthesized (14% yield) by treating 3,4-dihydro-6,7-dimethoxyisoquinoline (XI) with XII in refluxing alcohol. More recently, Beke and Szantay[23] similiarly prepared IX (83% yield) by a Michael condensation between XI·HCl and XII, cyclizing the product directly with base. Only one racemate with the proper stereochemistry for emetine (I) was isolated. Openshaw and Wittaker[24] independently synthesized IX (75%) by treating XI with the Mannich base methiodide XIII in refluxing alcohol.



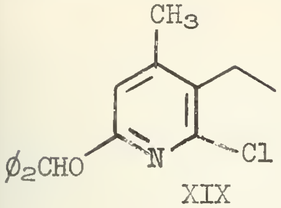
The next step in synthesizing natural emetine from the intermediates VI or IX involves introduction of an acetic acid moiety at C-2 with the necessary 2,3-trans-configuration. Battersby and coworkers[18], in the first stereospecific synthesis of (-)-emetine (I), accomplished this transformation by reducing the dioxopiperidine VI either catalytically or with borohydride to give a mixture of alcohols. The alcohols were then acetylated, and on heating with sodium acetate underwent a β-elimination to give the desired dihydropyridone (XIV). The reversible conditions of a Michael condensation of XIV with diethyl malonate gave the thermodynamically more stable trans diester (XV), which after hydrolysis, decarboxylation and re-esterification led to XVI. Cyclization of XVI with phosphoryl chloride gave the benzoquinolizidinium salt (XVII), which on catalytic hydrogenation gave the product (XVIII) arising from alpha addition of hydrogen to the iminium bond, as expected. That the racemic intermediate XVI possessed the desired stereochemistry for emetine (I) was shown by comparing the racemic intermediate XVIII with an identical but optically active ester derived from protoemetine. Thus, three of the four asymmetric centers of natural emetine had been introduced stereospecifically.



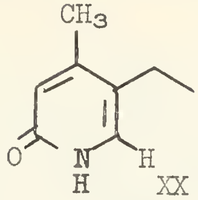


Employing a non-stereospecific approach, Osbond and coworkers[17,25] performed the same conversion of VI to XVI by treating the racemic intermediate VI with cyanoacetic acid to obtain a mixture of unsaturated nitriles which on hydrolytic esterification, reduction, and hydrolysis gave two diastereoisomeric acids (XVI, R=H), in 56% (trans-2,3) and 12% (cis-2,3) yields, whose stereochemistry was established later on in the synthesis and by subsequent work.[26] In still another admittedly more laborious approach to XVI which did not involve generation of VI via Ban's synthesis,[16] Osbond and coworkers[17,25] treated 2,6-dichloro-5-ethyl-4-methylpyridine with one equivalent of sodium diphenylmethoxide to obtain the benzyl ether XIX, which on hydrogenolysis gave predominantly the desired pyridone XX. This was treated with 3,4-dimethoxyphenethyl iodide and the alkylated product (XXI) condensed with ethyl oxalate to give XXII, which was hydrolyzed, treated with alkaline hydrogen peroxide, and decarboxylated to XXIII.

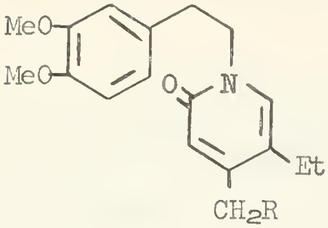
Hydrogenation with Adams catalyst gave the same diastereoisomeric acids obtained above.



XIX



XX

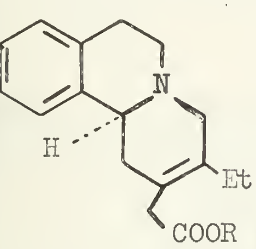


XXI, R = H

XXII, R = CO•COOEt

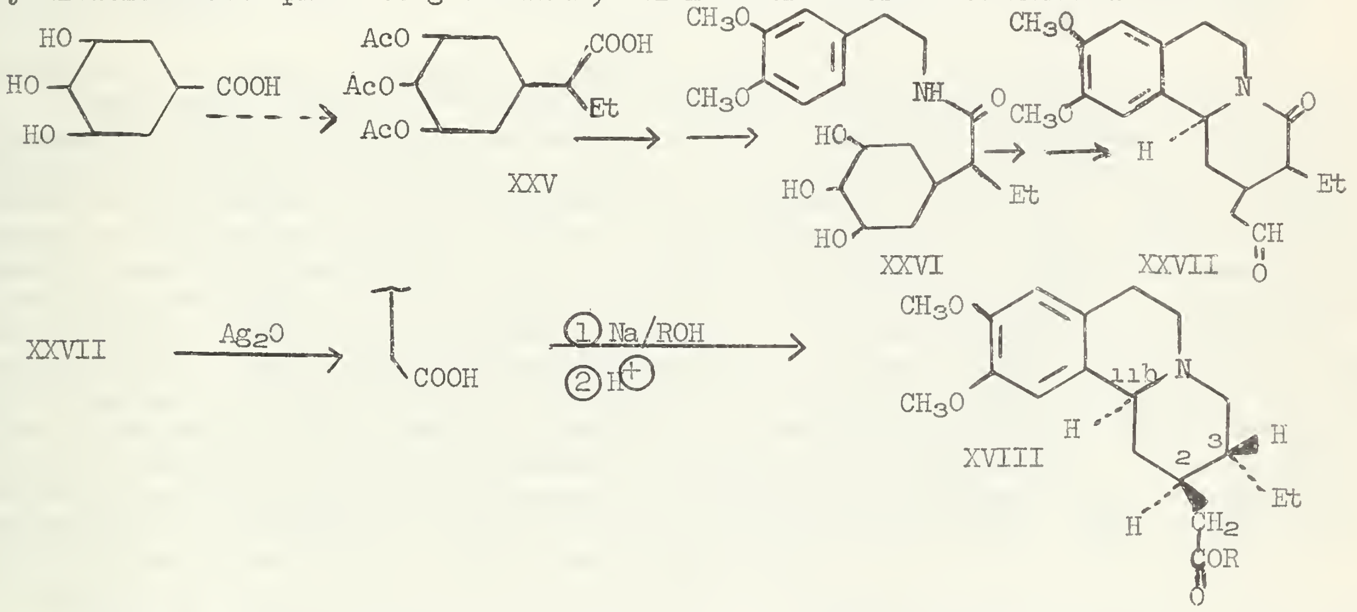
XXIII, R = COOH

In order to test the biological activity of various synthetic intermediates and to enable a synthesis of all eight of the theorectically possible emetine racemates to be designed, Brossi and coworkers[21,22,27,28-31] synthesized XXIV by treating IX with malonitrile followed by acid hydrolysis, thereby removing two of the three asymmetric centers of XVIII. This eventually led to compounds which Brossi called "rac-2-dehydroemetine" (XXXII) and "rac-2-dehydroisoemetine". The n.m.r. spectrum of XXIV showed no olefinic proton signals[30] and a synthetic verification for the structure given was supplied by Ritchie, Walker, and coworkers[40] who prepared XXIV via another route in the course of their emetine synthesis. Grüssner and coworkers[32] have also published a most arduous procedure leading to XVIII.



XXIV

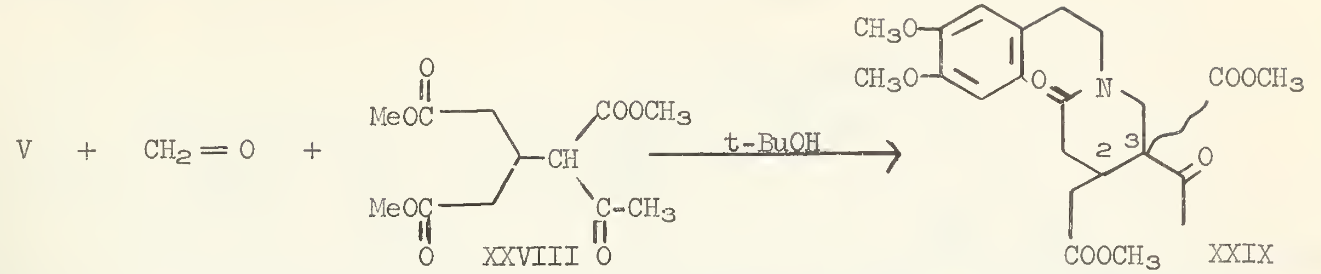
A route which leads to three isomers of XVIII but which proceeds in adequate yield to be a useful synthetic method has been reported by Burgstahler and Bithos.[33] Their intermediate XXV derived from hexahydrogallic acid is condensed with homoveratrylamine (V) followed by acid hydrolysis to give XXVI. When this is treated with hydroiodic acid followed by warming with phosphoric acid, cleavage of the glycol and subsequent cyclizations take place to give XXVII, which is transformed to XVIII as shown.



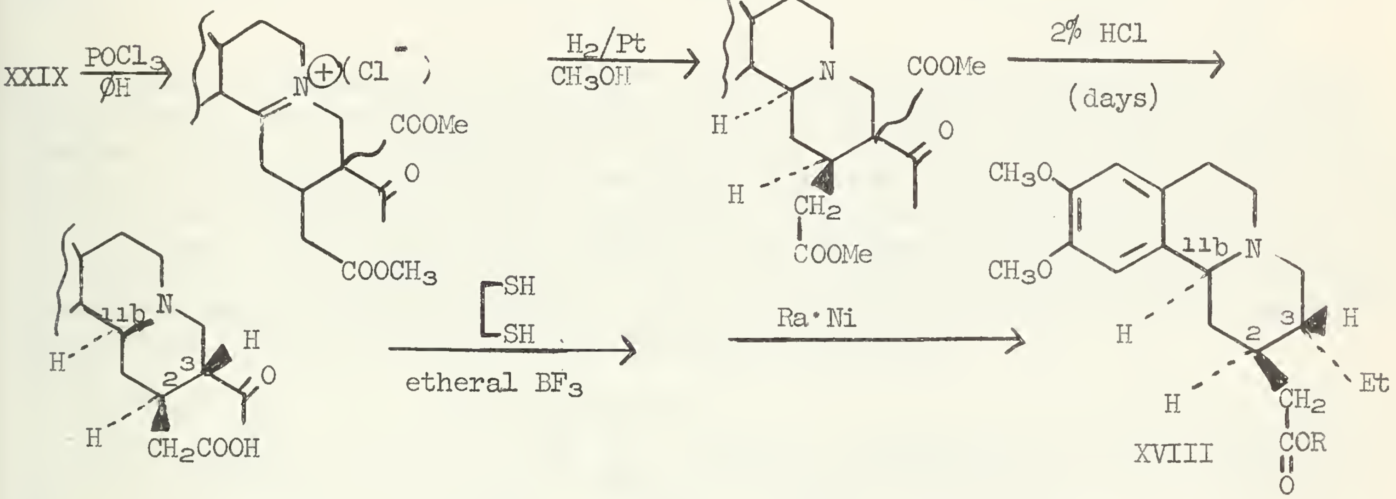
The most direct approach for introducing the acetic ester moiety at C-2 of IX was use of the Wittig reaction. Openshaw and Wittaker[34] treated IX with methoxycarbonylmethylenetriphenylphosphorane followed by hydrogenation which gave the desired 2,3-trans product (XVIII). In a recent communication, Szantay, Toke, and Kolonits[35] reported a similiar transformation from IX with potassium tert-butoxide in dimethylformamide and the phosphonate, $ROOCCH_2\overset{O}{\overset{\|}{P}}-(OEt)_2$, to obtain cis- and trans-olefins. Stereoselective hydrogenation in acidic methanol of each olefinic isomer separately gave 2,3-cis and trans-XVIII, shown by comparison with authentic material.[29,30,31]

In 1963, van Tamelen, Schiemerz, and Arons[36] announced an elegant synthesis of emetine (I), the necessary stereochemistry being established as a consequence of reactions which gave the more thermodynamically stable product. Such reasoning made possible the desired parallelism between the laboratory and proposed biogenetic synthetic pathways[1,13] to the natural alkaloid. Thus, in one step the appropiately substituted C ring of emetine was constructed (XXIX) by means of a Mannich condensation between

homoveratrylamine (V), formaldehyde, and the keto-triester (XXVIII).

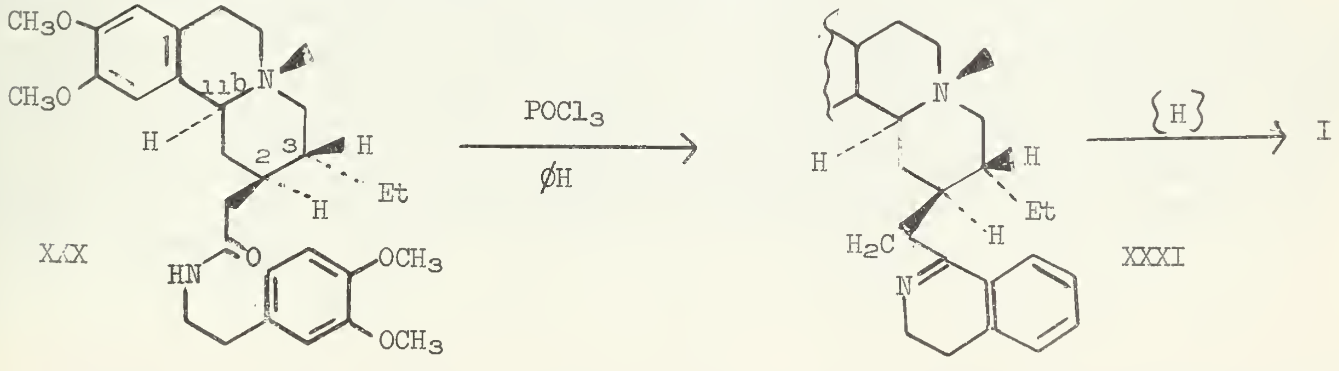


By the following series of conversions, the intermediate XXIX was transformed into XVIII, (R = H).



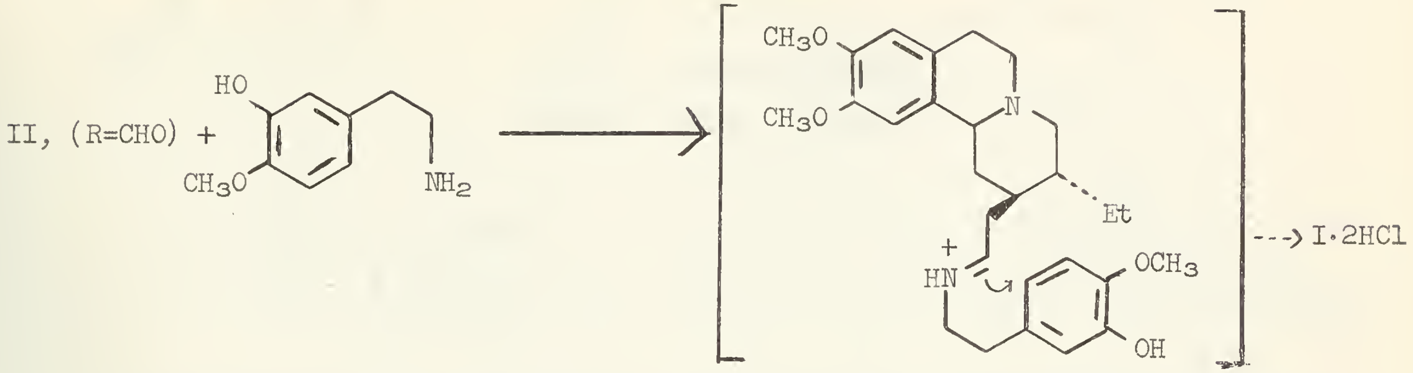
Attempts to shorten this reaction sequence even further were without success.

Since three of the four asymmetric centers of emetine are contained within the benzoquinolizidine portion of the molecule (XVIII), addition of the D and E rings (3,4-dihydro-6,7-dimethoxyisoquinoline moiety (XI) to the racemic intermediate inevitably leads to $(\pm)$-emetine (I) and $(\pm)$-isoemetine (epimeric to I at C-1'). Thus, the concluding stages of the emetine syntheses discussed thus far differ only in the method of attachment of homoveratrylamine (V) to the C-2 acetic acid moiety of XVIII or an analogue. The usual approach employed in the above syntheses has been formation of the amide XXX followed by ring closure with phosphorus pentoxide, phosphoryl chloride, or phosphorus pentachloride. This results in another alkaloid, $(\pm)$-O-methylpsychotrine (XXXI). Using this approach, the most efficient procedure is to treat the triethylamine salt of XVIII, (R=H) with ethyl chloroformate to form the mixed anhydride (XVIII, R= COOEt) which is in turn condensed with homoveratrylamine to yield the $(\pm)$-amide, XXX. In Battersby's hands,[18] cyclization gave 80% of racemic XXXI which was resolved, and as the free base hydrogenated in ethanol to yield 55% of (-)-emetine from (+)-XXXI. This hydrogenation was the only nonstereospecific step in their synthesis.

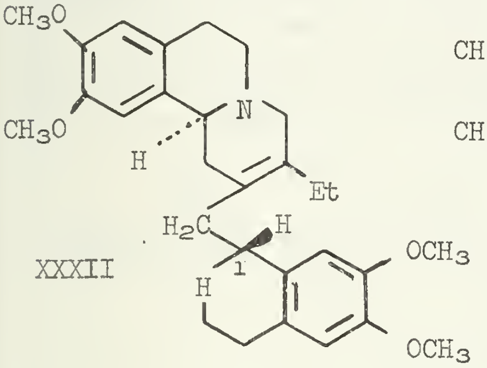


Szantay and Toke[37] in a most elegant fashion reduced XVIII with diisobutylaluminum hydride[38] to the alkaloid $(\pm)$-protoemetine (II, R=CHO) which was then allowed to react with β-3-hydroxy-4-methoxyphenethylamine and the resulting Schiff base was allowed to stand in acid solution. The cyclized base was isolated and treated with diazomethane

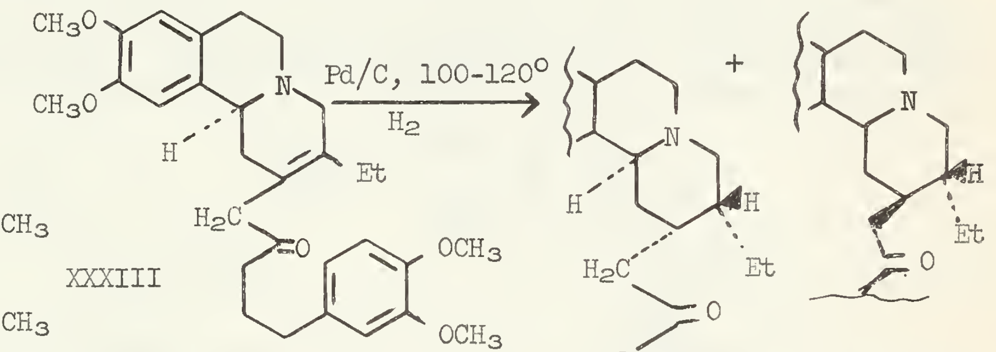
and the product finally isolated as the dihydrochloride of racemic emetine (I).



Brossi and coworkers[21,27,29,30,31] showed that "rac-2-dehydro-emetine", (XXXII) and analogues with various substitutents in the isoquinoline moiety exhibit high biological activity but compounds substituted in the 3 position with groups other than ethyl and all derivatives of the isoemetine series show little or no activity. To date these workers[26,28,29,30,31] have prepared and physically characterized all of emetine's stereoisomers. Their synthesis of natural emetine from XXIV was accomplished by first condensing with homoveratrylamine (V) to form the amide XXXIII which gave two saturated diastereoisomers on reduction XXXIV A and B, the B-racemate giving racemic O-methylpsychotrine (XXXI) on treatment with phosphoryl chloride.



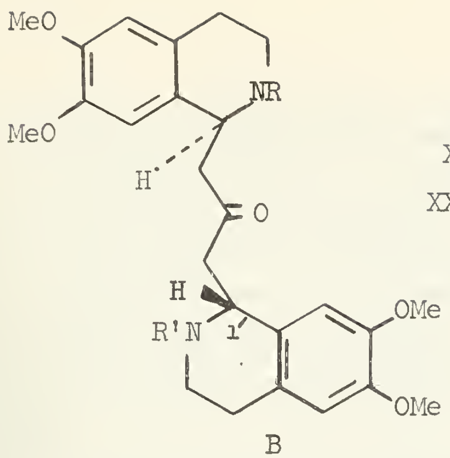
XXXII



XXXIV-A XXXIV-B

$$\text{XXXIV-B} \xrightarrow{POCl_3} \text{XXXI}$$

In each of the syntheses discussed thus far, the tetrahydroisoquinoline system (containing the asymmetric center C-1') has been fabricated only after the conformationally related three asymmetric centers in the benzoquinolizidine portion of emetine were introduced. In order to synthetically establish a relation between C-1' and the asymmetric center C-11b, Ritchie, Walker, and coworkers[39,40,41] devised an emetine synthesis whose key intermediate was XXXV-B. Utilizing the studies of Schöpf and coworkers[42] on condensation reactions of active methylenes and pseudo-bases, both interconvertible diastereoisomers of XXXV (A and B) were obtained by treating two equivalents of XI with one of acetonedicarboxylic acid. Racemic XXXV-A could be converted to meso-XXXV-B in aqueous sulfuric acid. Reduction of the N,N'-dibutyryl derivatives (XXXVI) with sodium borohydride gave two stereoisomeric alcohols in the case of the B compound and only one alcohol was isolated from reduction of the A racemate. Therefore, the meso-B form relates to the stereochemistry of natural emetine (I) and likewise the A form to isoemetine.



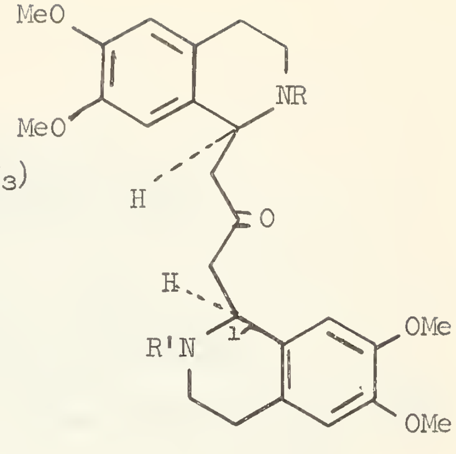
B

XXXV, (R=R'=H)

XXXVI, (R=R'=COnPr)

XXXVII, (R=R'=$\mathrm{CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3}$)

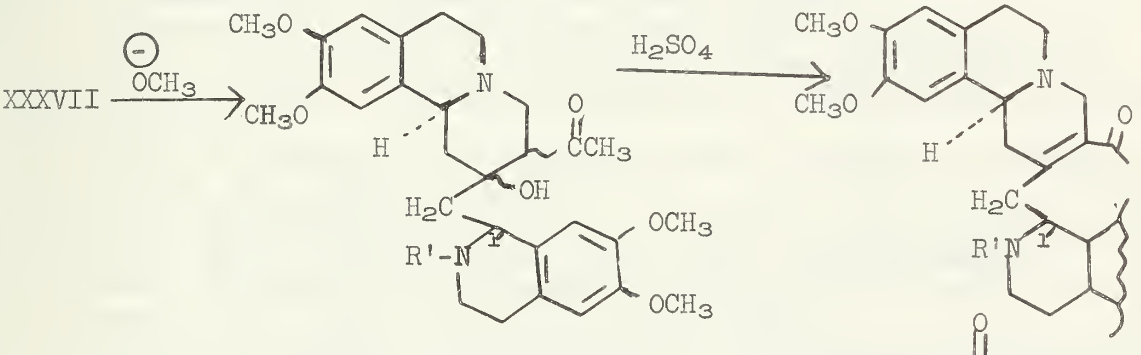
XXXVIII, (R=H, R'=$\mathrm{CH_2}\phi$)



A

The diastereoisomeric ketone XXXV-B when treated with methyl vinyl ketone in methylene chloride for two hours gave predominantly the adduct XXXVII-B. Unfortunately, the A isomer was the thermodynamic product, and when the Michael condensation was allowed to proceed for a longer period (ca. 24 hours) a mixture of the adducts XXXVII-A (65 %) and XXXVII-B (15%) was obtained, regardless of the isomer of XXXV employed.

The diastereoisomeric triketones, XXXVII, were cyclized to the alcohols XXXIX (A and B) which were dehydrated, without inversion, to the corresponding diastereoisomeric conjugated ketones (XL, A and B). The same transformations were carried out on the unsymmetrical N-benzyl ketones (XXXVIII, A and B), which were not interconvertible. Thus, Michael condensation with methyl vinyl ketone followed by methoxide cyclization and dehydration gave, stereospecifically, the two diastereoisomeric conjugated ketones (XLI)-A and (XLI)-B, respectively. Conversion of XL-B to XLI-B was effected by formation of the quaternary salt with benzyl bromide followed by a mild Hofmann degradation.



XXXIX, R'=$\mathrm{CH_2CH_2\underset{O}{\underset{\|}{C}}CH_3}$

XL, (R'=$\mathrm{CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3}$)

XLI, (R'=$\mathrm{CH_2}\phi$)

A=(C-1', H_α)

B=(C-1', H_β)

Spectroscopic data were in agreement with the general structures of the intermediates. Birch reduction (lithium in ammonia) of XLI-B followed by equilibration in acid was stereospecific in this case since subsequent removal of the ketone group by formation of the dithioketal followed by Raney nickel desulfurization led to (±)-N-benzylemetine. Hydrogenolysis of the benzyl group gave racemic natural emetine (I) which had the same physical properties (R_f value and infrared spectrum) as the natural alkaloid and half its biological activity against Entamoeba histolytica. Resolution was effected with N-acetyl-L-leucine[21] and the (-)-emetine (I) recovered was identical with the natural alkaloid. The A racemate likewise gave (±)-isoemetine.

Removal of the ketone and benzyl groups of XLI-B prior to Birch reduction gave "rac-2-dehydroemetine" (XXXII) which had the same infrared and ultraviolet spectra, biological activity, and R_f value of the hydrochloride salt as those recorded by Brossi and coworkers.[27,30f]

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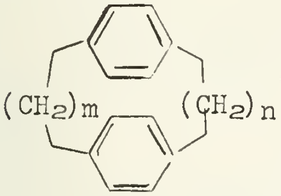
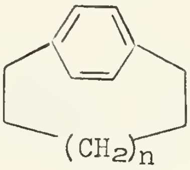
PARACYCLOPHANES

Reported by Ping C. Huang December 4, 1964

Introduction: Paracyclophane was the name suggested by Cram[1] for the class of compounds which have benzene rings linked at the para positions by polymethylene bridges. I is designated an [m,n]paracyclophane and II an [n]paracyclophane. The study of these compounds is of interest because they offer unique transannular electronic and steric effects on physical and chemical properties. When m and n are small, spectral abnormalities, particularly in the ultraviolet region, transannular substituent effects, optical isomerism and modified reactions in the bridges have been observed as compared to the open-chain model compounds. The chemistry of paracyclophanes has been the subject of several reviews.[2,3,4] This seminar will emphasize the results of more recent investigations.

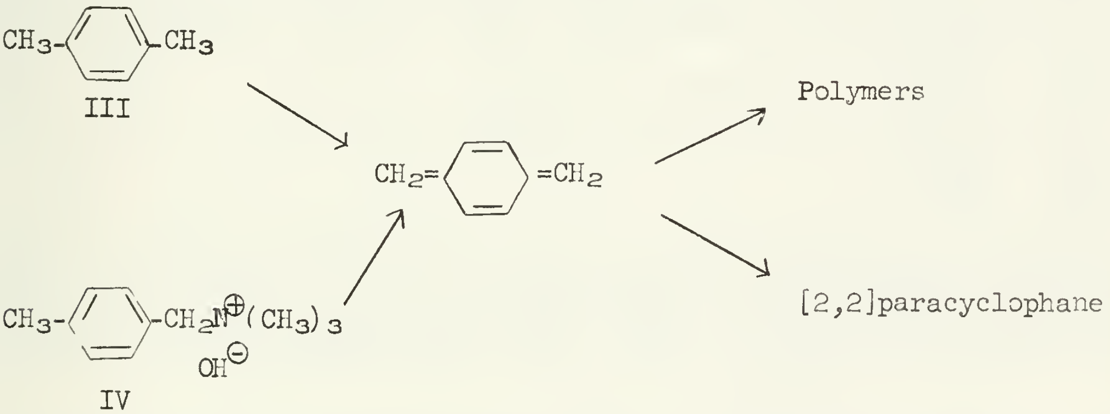


I

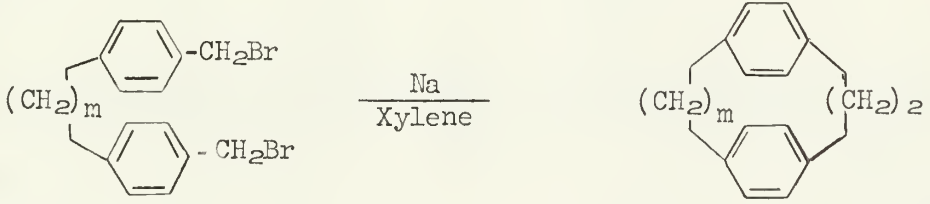


II

Synthesis: [2,2]paracyclophane, the lowest homologue of type I synthesized, was first prepared[5] in trace amount on pyrolysis of p-xylene (III). Errede[6] improved the method using fast flow pyrolysis under low pressure and subsequent instantaneous condensation of the pyrolysis products into a solvent maintained at -78° C. It was also synthesized[7] in 17% yield by the low temperature (60°-100° C) decomposition of p-methylbenzyltrimethylammonium hydroxide (IV).

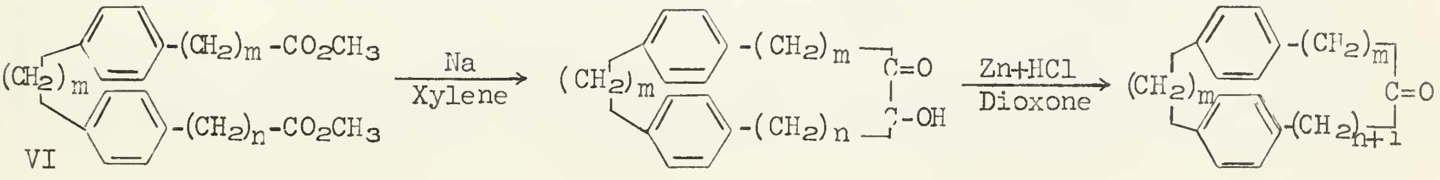

CH_3
CH_3
III
$CH_2=$
$=CH_2$
Polymers
[2,2]paracyclophane
CH_3
$CH_2N^{\oplus}(CH_3)_3$
$OH^{\ominus}$
IV

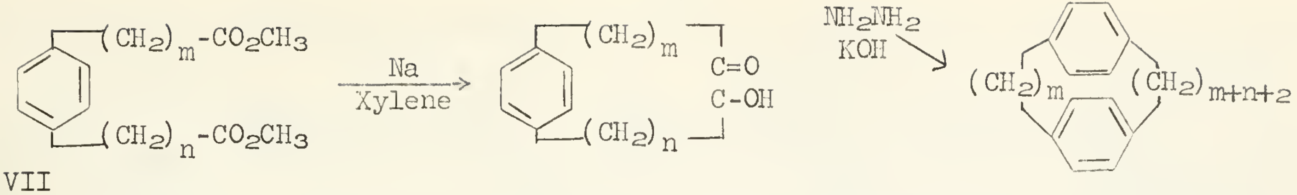
Phenothiazine as polymerization inhibitor increased the amount of dimer formed. [m,2]paracyclophanes have been synthesised[1] in about 3% yield by high dilution intramolecular Wurtz reactions. The reaction failed when other than a bis-benzyl bromide (V) was employed.


$-CH_2Br$
$(CH_2)_m$
$-CH_2Br$
Na
Xylene
$(CH_2)_m$
$(CH_2)_2$

V

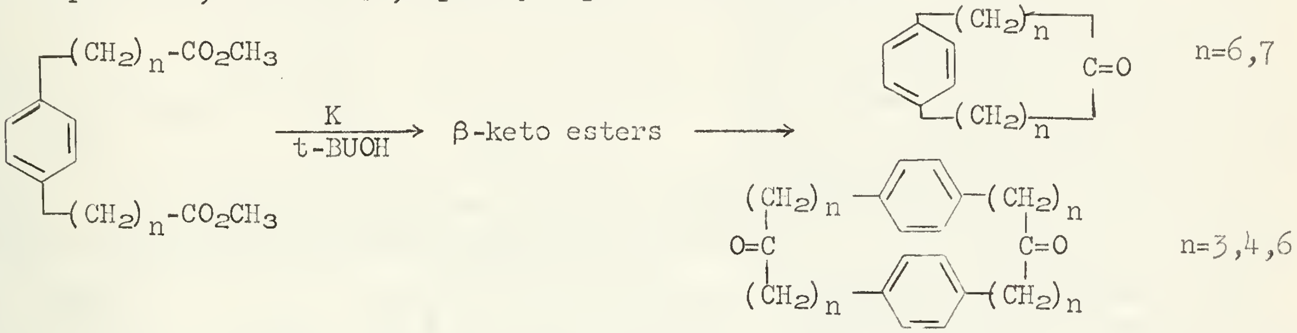
The acyloin condensations of (VI) and (VII) have been used to synthesis [m,n]-paracyclophanes and [n]paracyclophanes, respectively.[1]


$-(CH_2)_m-CO_2CH_3$
$(CH_2)_m$
$-(CH_2)_n-CO_2CH_3$
VI
Na
Xylene
$(CH_2)_m$
$-(CH_2)_m$
C=O
C-OH
$-(CH_2)_n$
Zn+HCl
Dioxone
$(CH_2)_m$
$-(CH_2)_m$
C=O
$(CH_2)_{n+1}$

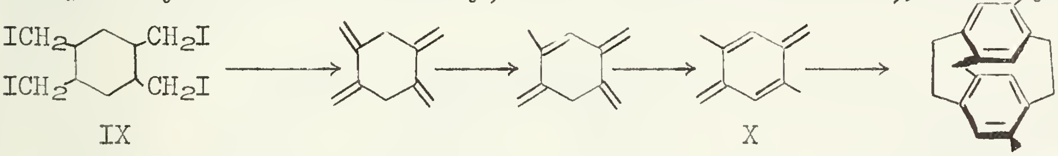

(CH2)m-CO2CH3
(CH2)n-CO2CH3
Na
Xylene
(CH2)m
C=O
C-OH
(CH2)n
NH2NH2
KOH
(CH2)m
(CH2)m+n+2

VII

Dieckmann cyclization of the esters of p-phenylenedicarboxylic acids (VIII) gave ketone derivatives of [n]paracyclophanes. In cases where intramolecular cyclizations were impossible, dimeric [m,n]paracyclophanes were formed.[8]

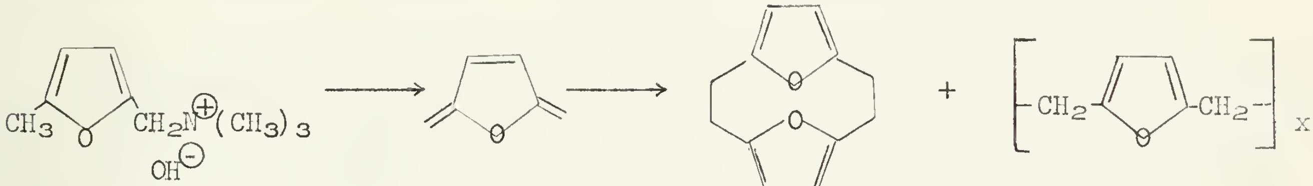

(CH2)n-CO2CH3
(CH2)n-CO2CH3
K
t-BUOH
β-keto esters
(CH2)n
C=O
(CH2)n
n=6,7
(CH2)n
O=C
(CH2)n
(CH2)n
C=O
(CH2)n
n=3,4,6

The reaction was desirable for making compounds with odd-numbered carbon bridges from symmetrical p-phenylenedicarboxylic esters, which have led to compounds with even-numbered carbon bridges in the acyloin condensations. Longone and Bottcher[9,10] reported a nonaromatic route to paracyclophanes. Dehydroiodination of 1,2,4,5-tetrakis-(iodomethyl)-cyclohexane (IX) with base gave a relatively high yield (25%) of the tetramethyl[2,2]paracyclophane (XI). The reaction was believed to give 1,2,4,5-tetramethylenecyclohexane initially, which isomerized[11] to 2,5-dimethyl-p-xylylene (X), which finally dimerized to form the product (XI).


ICH2
CH2I
ICH2
CH2I

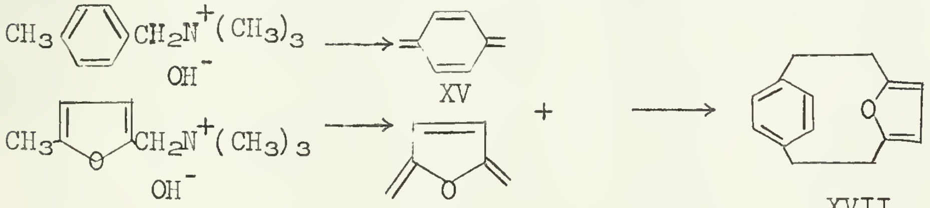
IX X XI

Pyrolysis of 5-methyl-2-furfuryl-trimethylammonium hydroxide (XII) has been found[7] to give 2,5-dimethylene-2,5-dihydrofuran (XIII). (XIII) was isolated at -78° C, and when warmed in the presence of polymerization inhibitors, it dimerized in high yield (72%) to form the heterocyclophane, 5,5'-ethylene-1,2-di-(2-furyl)ethane (XIV). Similar results were obtained with thiophene analog of the furan quaternary hydroxide.


CH3
CH2N⊕(CH3)3
OH⊖
+
CH2
CH2
x

XII XIII XIV

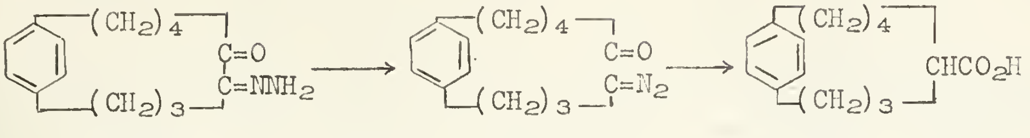
Cram[12] utilized the synthesis of p-xylylene (XV) and 2,5-dimethylenedihydrofuran (XVI) to form the hetrocyclophane (XVII) by the cross breeding reaction formulated. Treatment of (XVII) with bromine in methanol at -30° C, then with water and followed by Clemmensen reduction gave the highly strained [8]paracyclophane. Allinger[13] obtained the same product by a procedure of greater generality.


CH3
CH2N+(CH3)3
OH-
CH3
CH2N+(CH3)3
OH-
+

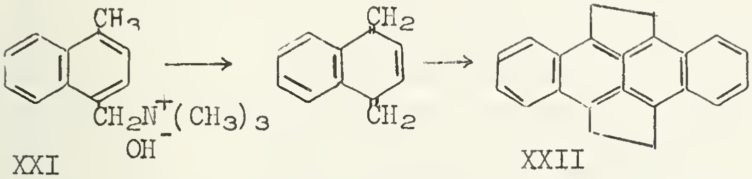
XV XVI XVII

4,5-Diketo-[9]-paracyclophane (XVIII) was oxidized with manganese dioxide to give the diazoketone (XIX). The latter was not isolated, but photolysis[14] gave the 4-carboxy-[8]paracyclophane (XX) in 25% yield. The naphthalene analog of [2,2]-

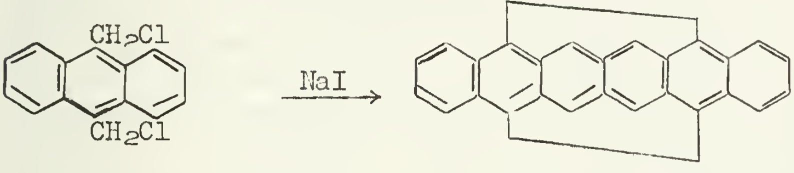
paracyclophane, [2,2]paracyclonaphthane (XXII) has been synthesized[15] in 3% yield by an elimination-cycloaddition reaction with 4-methyl-1-naphthyl-trimethylammonium hydroxide (XXI). The anti-configuration of the product was confirmed by preparing the same isomer via a 9-step sequence from [2,2]paracyclophane in 0.07% yield. Production of the anti-isomer in the 1,6-to-1,6-cycloaddition reaction indicated that unlike the Diels-Alder reaction, π,π interactions were minimized in the transition state. Reaction of sodium iodide with 9,10-di(chloromethyl)anthracene (XXIII) in acetone gave tetrabenzo[2,2]paracyclophane (XXIV) in 63% yield. The product was obtained similarly for 9,10-di-(bromomethyl)anthracene.[17] The formation of the dimer instead of the expected diiodo-compound was analogous to the preparation of benzocyclobutanes from ω,ω'-dibromo-o-xylenes by the action of sodium iodide.[18] Recently, a multilayered [2,2]-paracyclophane (XXVIII) has been synthesized[19] from tetramethyl[2,2]paracyclophane (XXV). Reaction of (XXV) with N-bromosuccinimide yielded the bromomethyl compound (XXVI), which was converted to the Hofmann base (XXVII). Pyrolysis of (XXVII) in a toluene-water medium gave the product (XXVIII).



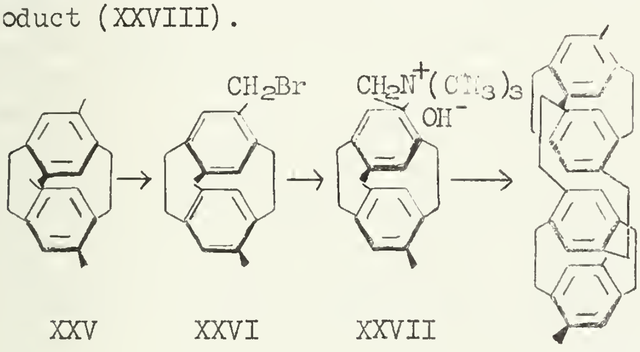
XVIII XIX XX



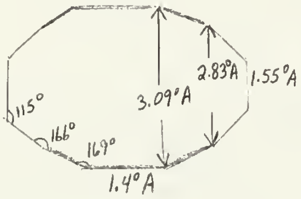
XXI XXII



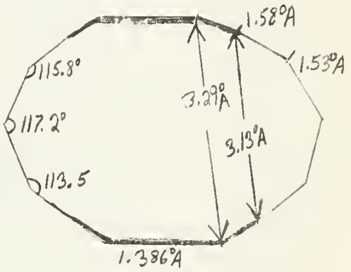
XXIII XXIV



XXV XXVI XXVII XXVIII



XXIX



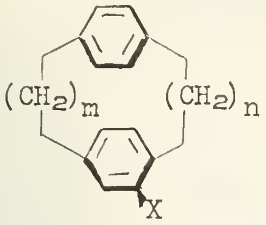
XXX

Molecular Structure and Specta: The crystallographic structure of [2,2]paracyclophane (XXIX)[20] and [3,3]paracyclophane (XXX)[21] have been determined. The bond angles and distances which were observed are indicated in the profile of the molecule sketched. The structures established that strong repulsive forces exist between the benzene rings which thrust the rings apart and distort the two benzene nuclei from their normal planar configurations. The crystallographic study of [3,3]paracyclophane revealed that the benzenes are not only bent, but also considerably displaced from the centered position found in the more rigid [2,2]paracyclophane. In the [n]paracyclophane series, Allinger (13) has estimated the deformation angle θ of the distorted boat-shape benzene ring from regular planar configurations to be $\theta = 20^\circ$ for n=8, 15° for n=9 and about 5° for n=10 and 12. Cram[22] has used scale molecular models to measure the idealized distances between the two benzene rings of the [m,n]paracyclophanes and found that for the methylene bridges smaller than [4,4], the inter-ring distances were shorter than 3.4 Å, which is the normal inter-ring distance in crystals of stacked aromatic nuclei.[23] Those [m,n]paracyclophanes whose methylene bridges were smaller than [4,4] were found to give abnormal ultraviolet absorption spectra as compared with the open-chain model compounds. Shifts of both long and short wavelength bands to longer wavelengths were observed. These abnormal spectra were interpreted as being associated with two effects: the bending of the benzene rings from their normal planar configurations and transannular interaction between the π-electrons of the two benzene rings in the excited states of the molecules.[22,24] Similar results were observed in

the [n]paracyclophanes as n decreases from 12 to 8, attributed to the distortion of the benzene ring from planarity.[13,25] Additional evidence for transannular electronic effects in the paracyclophanes was found in the visible spectra of the one-to-one tetracyanoethylene paracyclophane complexes.[26] A correlation has been observed between the long wavelength absorption band of the tetracyanoethylene-alkybenzene π-complexes and the electron-releasing ability of the π-base of the complexes.[27] In these complexes, the stronger the base, the longer the wavelength of the absorption maximum of the complex. All of the tetracyanoethylene-paracyclophane complexes absorbed at longer wavelengths than the open-chain model compounds such as 1,3-bis-(4-ethylphenyl)propane. The decrease in the λ max of the complexes was in the order [3,3]>[3,4]>[1,7]>[2,2]>[1,8]>[2,3]>[4,6]>[9]>[12]>[6,6]>[1,10]>[5,5]>[2,4]>[4,4]>model compounds. This order represented the balance between two opposing effects. Deformation of the complexed benzene ring and its benzyl carbons from their normal coplanar state would cut down the amount of electron release of the π-base to the π-acid and transannular electron release of the other ring to the complexed benzene ring would enhance electron release of the π-base to the π-acid. These two effects provided a maximum of π-electron availability in [3,3]paracyclophane. The π-π repulsions were probably strongest when the benzene rings were electronically equivalent, as in the non-complexed state. When one ring became π-bonded to a tetracyanoethylene molecule, that ring became slightly electron deficient, the π-π repulsions between rings decreased, the rings became more centered and bond angle strain was released. The same type of effect made [3,4]paracyclophane a stronger π-base than [2,2]paracyclophane, whose rigidity mitigated against such distortion. The fact that the complex of [6,6]paracyclophane absorbed at longer wavelengths than the complex of [4,4]paracyclophane suggested that in the former compound, the methylene bridges were enough longer to allow the two benzene rings closer than in the [4,4] compound, in which the relatively inflexible methylene bridges held the rings apart. Pariser and Parr[28] have shown that the ultraviolet spectrum of benzene could be calculated to a fair approximation utilizing the idea of a core Hamiltonian and accounting for the interactions of the separate π-electrons with the core and with each other. The key to the solution of the problem lies in the empirical evaluation of certain integrals. Subsequently, Schiess and Pullman[29] showed that with some small numerical modifications of the procedure, an excellent fit of the calculated values and the observable portion of the spectrum could be made. The energy spectrum of the singlet and triplet monoexcited states of a simple model of [n,n]paracyclophanes, in which nondeformed benzene rings were considered as parallel and the centers lie on the straight line perpendicular to the plane of the benzene rings, was calculated by this method using limited configurational interaction.[30] An improved agreement with the experimental spectra was obtained when the resonance integrals between all the atoms of the planar model[31], the effect of mutual shift of the benzene rings and the effect of benzene ring distortion were considered.[32,33] A similar calculation for the [n]paracyclophanes has also been reported.[13]

In the nuclear magnetic resonance spectra, the aromatic protons of [m,n]paracyclophanes appeared at higher field than in the open-chain model compounds.[15] In o-substituted [2,2]paracyclophanes, one of the aromatic protons stood apart and was upfield of the others when the substituent was electron releasing and downfield when the substituent was electron withdrawing.[35] This proton was assigned as the hydrogen ortho to the functional group. The other aromatic hydrogens exhibited considerable fine structure, but their "center of gravity" still appeared at higher field than in the open-chain model compounds. In the n.m.r. spectra of the [1,n]paracyclophanes, the aromatic protons of the [1,12]compound appeared as a singlet at normal a value (τ2.97). As n decreased, the singlet split into multiplets, whose center moved upfield. The coupling constants associated with this splitting increased from 2.5 cps with n=11, 4.0 cps with n=9 and 10 to 6.5 cps where n=8. This splitting and movement to higher fields was believed[35] due to shielding of the aromatic protons ortho to the benzhydryl position by the induced magnetic field in the transannular benzene ring. The nonbenzyl methylene hydrogens were better resolved in the more rigid smaller bridge compound. The methylene hydrogens of [1,8]paracyclophane exhibited three groups of absorptions whereas the others gave only two groups of absorptions at fields lower the greater the value of n. This shift to higher field with decreasing value of n was attributed to increasing shielding of the methylene hydrogens by the induced magnetic fields of the

two rings. Similar observations were found in the [n]paracyclophanes.[36] Molecular dissymmetry arising from restricted rotation about single bonds at ordinary temperatures was observed in some of the monosubstituted [m,n]paracyclophanes (XXXI).[37,38] The racemization rate of the sodium salt of [3,4]paracyclophane-5-carboxylic acid at 160° was about $10^{-4}\sec^{-1}$, corresponding to about 50 kcal/mole for the activation energy of racemization. A monosubstituted [n]paracyclophane, [10]paracyclophane-12-carboxylic acid has been resolved into pure optical antipodes through its cinchonidine salts.[39,40] The active forms racemized at an appreciable rate at room temperature in the solid, crystalline state.



XXI

m=n=2; m=3,n=4 resolved
m≥4, n≥4 nonresolved
where X=-COOH,-Br, etc.

Transannular Substituent Effects in π-π Complexes of Paracyclophanes: The spectral properties of π-π complexes between 13 monosubstituted [2,2]paracyclophane and tetracyanoethylene (TCNE) have been examined.[34] The position of λ max of the longest charge transfer bands of the complexes was used as a measure of the relative π-base strengths of the substituted paracyclophanes. The equilibrium constants of the one-to-one complex of the 4-ethyl, 4-acetyl and 4-cyano[2,2]paracyclophane and p-xylene measured at 25° C are shown in Table I. The equilibrium constant of the complex with [2,2]paracyclophane itself was estimated to be about 40. The data indicates an enhanced π-base strength for the paracyclophane system and a marked sensitivity to substituent effects. In the ethyl derivative, the electron-releasing character of the ethyl group would make the substituted ring the more basic, and the ring which is complexed. The electron-withdrawing character of the acetyl and cyano groups would deactivate the rings to which they are attached, and the unsubstituted rings are complexed. The fact that the acetyl and cyano complexes gave different equilibrium constants was evidence for transannular electronic effects of the substituents on the unsubstituted ring. For the electron releasing groups, a plot (Fig. 1) of the decrease in excitation energies for the charge transfer bands (ΔE_t) due to the substituent against one particular set of σ_A^{+}[41] gave a reasonably straight line for all except the hydroxyl and amino groups. These substituents themselves interacted with tetracyanoethylene. The σ_A^{+} values were calculated through the Yukawa and Tsuno's equation: $\sigma_A^{+}=\sigma + r(\sigma_B^{+}-\sigma)$ where σ is the Hammett constant, σ_B^{+} is the Okamoto-Brown constant[42] and r is a parameter which measures the importance of the resonance effect of the reaction in question. The σ_A^{+} values used in Fig. 1 involved an r-value of 0.25. With electron withdrawing groups, a plot (Fig. 2) of the increase in excitation energies (ΔE_t) due to the substituent against σ_m[43] gave poor linear relationships. Presumably the non-substituted ring was directly involved in these complexes. Although the correlation exhibited in Fig. 2 is very crude, a substituent effect of a transannular nature was suggested.[34]

Table I

Equilibrium Constants for TCNE-Aromatic Compound Complexes in Dichloromethane

Compound	λ_{max}(mμ)	($cm^{-1}m^{-1}l$)	K
4-Ethyl[2,2]paracyclophane	540	1610	52
4-Acetyl[2,2]paracyclophane	496	1450	24.5
4-Cyano[2,2]paracyclophane	475	2000	8
p-Xylene	460	2650	7.6

Hydrogen Deuterium Exchange of [1,n]paracyclophanes: The [1,n]paracyclophanes with n=8 to 12 and the open chain model compound 4,4'-dimethyldiphenylmethane have been subjected to potassium t-butoxide hydrogen deuterium exchange in t-BuOH.[35] Exchange occurred predominantly at the diarylmethylene position. The relative rate using the model compound as standard gave [1,12],[1,11], [1,10], [1,9], and [1,8] the order of 2; 2.3; 0.2; 0.06 and 0.0024, respectively. The data indicate that the kinetic acidities of the diarylmethylene hydrogens of the [1,n]paracyclophanes are comparable to those of their open chain model when n is 11 or 12. A drop by a factor of 10 occurred in passing from n=11 to 10 and a further drop by a factor of 3 when n=9.

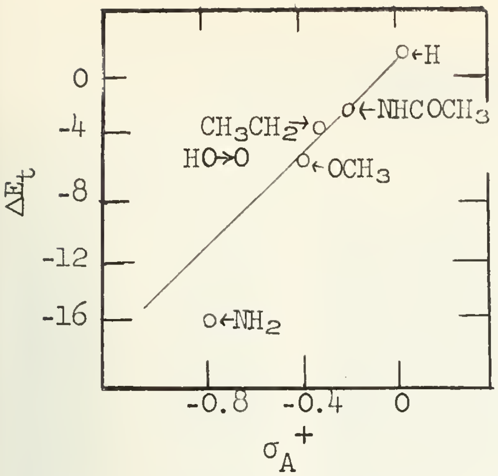


Fig. 1. - Plot of differences in transition energies between substituted and non-substituted [2,2]-paracyclophane-TCNE complexes (ΔE_t) against σ_A^+ values for electron-releasing substituents.

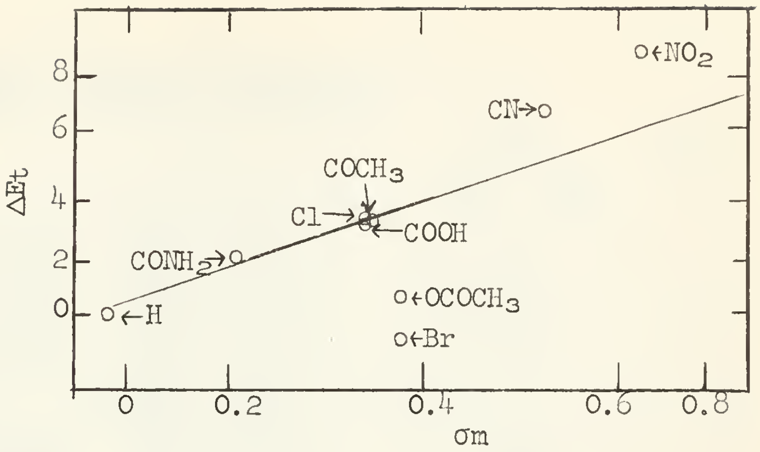
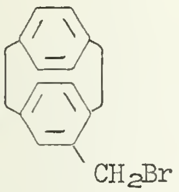


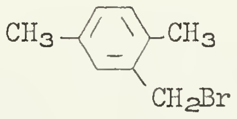
Fig. 2. - Plot of differences in transition energies between substituted and non-substituted [2,2]paracyclophane-TCNE complexes (ΔE_t values) against σ_m values for electron-withdrawing substituents.

With n=8 the rate declined by an additional factor of 25. As the angle between the benzene rings and the diarylmethylene carbon decreased with decreasing n, the p-character of the aryl methylene bonds increased to accommodate the strain and the s-character of the carbon-hydrogen bonds increased, which would be expected to make the protons more acidic. The enchanced acidity of cyclopropane[44] compared to its larger homologs was attributed to similar causes. The effect in the [1,n]paracyclophanes was apparently buried by some larger effect. It was believed[35] that the loss of conjugation of the carbanion with the aromatic nuclei as n decreased was responsible for the over all decreased rates of the lower homologs. Molecular models suggested less flexibility in benzene ring orientation in the [1,n]systems than in the open chain model. This fexibility decreased with decreasing n, until when n=8, coplanarity of the bonds to the benzhydryl anion and one of the benzene rings was no longer possible. An extreme example of the importance of the conjugation effect was found in the case triphenylmethane compared with triptycene.[45]

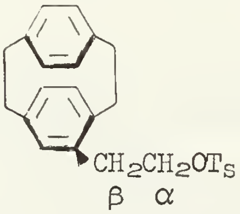
[2,2]Paracyclophanyl as a Neighboring Group: The ability of [2,2]paracyclophane to act as a neighboring group when attached to C_α or C_β of a carbonium-ion forming system has been determined through solvolysis reactivity comparison of compounds (XXXII), (XXXIII), (XXXIV), and (XXXV).[46]



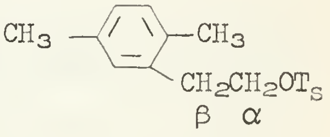
XXXII



XXXIII



XXXIV



XXXV

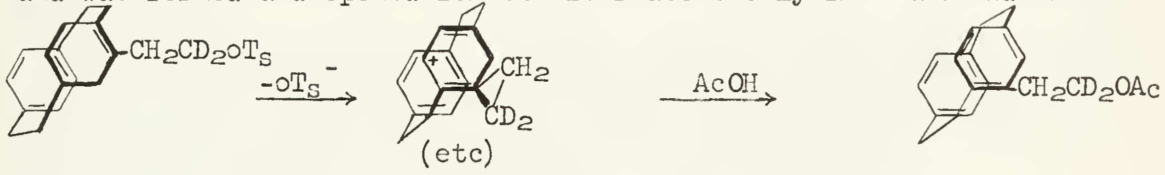
The rate constants and activation parameters for solvolysis of the compounds are listed in Table 2. The rate of hydrolysis of (XXXII) was 6 to 7 times faster than (XXXIII) in 80% dioxane-20% water and the entropy of activation of (XXXII) was less negative by 10 e.u. than (XXXIII). It has been established[47] that in solvolysis of β-arylethyl systems, the magnitude of the entropy of activation was a reliable indication of the balance between neighboring aryl and solvent participation in carbonium ion formation. Neighboring aryl group involvement correlated with $\Delta S^{\ddagger}$ values of -9 to -12 e.u. and ionization with solvent participation correlated with values -17 to -21 e.u. Although arylmethyl and not β-arylethyl was involved in the cases considered here, the data suggested a similar effect, in which charge delocalization was more

Table 2

Rate Constants and Activation Parameters for Solvents of (XXXII), (XXXIII), (XXXIV), and (XXXV)

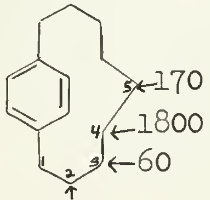
Compound	T, °C.	Solvent	$k \times 10^6$, sec.$^{-1}$	$\Delta H^{\ddagger}$, kcal. mole	$\Delta S^{\ddagger}$, e.u.
XXXII	34.6	80% dioxane-20% water	13.3 ± 1.5	21.1	-12
XXXII	52.4	80% dioxane-20% water	94.0 ± 0.40		
XXXIII	34.6	80% dioxane-20% water	2.33 ± 0.16	18.9	-22
XXXIII	52.4	80% dioxane-20% water	13.5 ± 1.3		
XXXIV	74.8	Acetic acid	5.11 ± 0.33	24.7	-11.7
XXXIV	110.5	Acetic acid	160 ± 9		
XXXIV	76.6	80% acetone-20% water	9.68 ± 0.31	23.2	-15.0
XXXIV	95.5	80% acetone-20% water	56.7 ± 2.6		
XXXV	74.9	Ethanol	11.1 ± 0.6	21.6	-18.8
XXXV	95.8	Ethanol	69.3 ± 3.8		
XXXV	74.8	Acetic acid	0.89 ± 0.08	26.1	-11.1
XXXV	110.5	Acetic acid	33.9 ± 1.2		
XXXV	76.6	80% acetone-20% water	2.33 ± 0.29	22.2	-20.2
XXXV	95.8	80% acetone-20% water	13.0 ± 1.7		
XXXV	74.9	Ethanol	4.61 ± 0.26	21.3	-21.4
XXXV	95.8	Ethanol	27.8 ± 1.9		

important in the ionization of (XXXII). The rate of hydrolysis, acetolysis and ethanolysis of (XXXIV) was 2.5 to 6 times that of (XXXV). In acetic acid, (XXXIV) gave nearly the same $\Delta S^{\ddagger}$ values as (XXXV), whereas in acetone-water and ethanol, $\Delta S^{\ddagger}$ values for (XXXIV) were less negative than for (XXXV). The data indicated that the paracyclophenyl group is better able to aid in ionization than is the 2,5-dimethylphenyl group. Deuterium at C_α in (XXXV) was found to be scrambled in the acetolysis (46% C_β-D) and hydrolysis (26% C_β-D) products. Deuterium at C_α in (XXXIV) was not disturbed during acetolysis of formolysis, in the latter case under conditions where carbonium ion was formed repeatedly. The experimental evidence suggested the existence of a unique bridged ethylenephenonium ion (XXXVI)[48] as intermediate which was unsymmetrical and was formed and opened for steric reasons only from the side remote from the transannular ring. The fact that paracyclophanyl was a better neighboring group than its open-chain model in both cases was attributed to delocalization of positive charge into the transannular ring in the transition states.

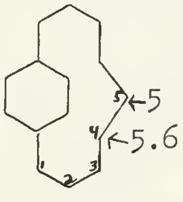


XXXIV XXXVI

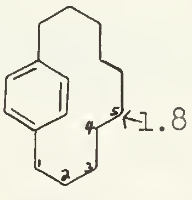
Acetolysis of [n]Paracyclophanyl Tosylate: The rates of acetolysis of [9]paracyclophanyl tosylate (XXXVII), [10]paracyclophanyl tosylate (XXXVIII), hexahydro[9]-paracyclophanyl tosylate (XXXIX) and hexahydro[10]paracyclophanyl tosylate (XL) with tosylate groups at different positions have been studied.[49] Using cyclohexyl tosylate as a standard, the relative rayes are shown as follows:



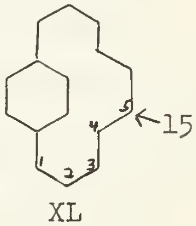
XXXVII



XXXVIII



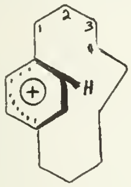
XXXIX



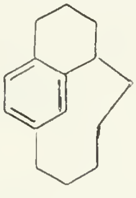
XL

The two hexahydro systems showed rate increases by factor of 5 to 15 over cyclohexyl tosylate. Some release of strain was believed to contribute in these small factors.

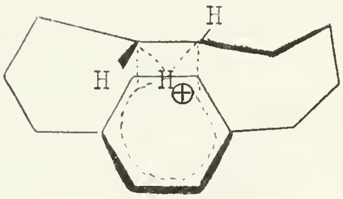
Molecular models suggested that the hexahydro system was more strained than the corresponding benzenoid system. Hexahydro[10]paracyclophane-5-tosylate (XL) solvolyzed 8 times as fast as [10]paracyclophane-5-tosylate (XXXIX) and the two hexahydro[9]paracyclophanyl tosylates (XXXVIII) solvolyzed faster than [9]paracyclophanyl-2-tosylate (XXXVII). The rate was also related to the distance from the tosylate group or the incipient carbonium ion to the face of the benzene ring. In [9]paracyclophanyl tosylate (XXXVII), the shortest distance involved the 2-position. The lack of acceleration for the 2-tosylate was believed due to the fact that the ethylenephenonium ion that would be formed by phenyl participation would tighten the methylene bridge to the point where the benzene ring would have to become seriously deformed. The next shortest distance involved 4-tosylate, which gave the greatest acceleration. The acetate was formed from optically active tosylate with complete retention of configuration and an optically active tricyclic hydrocarbon (XLII) byproduct was formed. The author suggested that a carbonium ion (XLI) was formed as an intermediate.



XLI



XLII



XLIII

In the case of [9]paracyclophane-5-tosylate, acetolysis gave no 5-acetate but the rearranged 4-acetate and the tricyclic hydrocarbon (XLII) byproduct. An intermediate carbonium ion with both phenyl and hydrogen participation (XLIII)[50] was postulated.

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MECHANISM OF THE THERMAL REARRANGEMENT OF CYCLOPROPANE

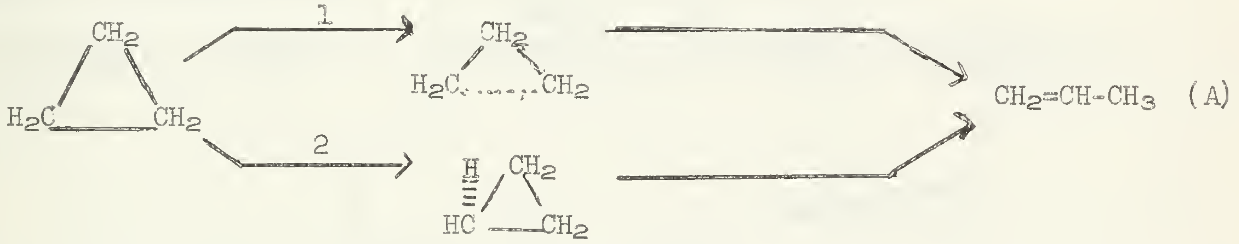
Reported by George Su December 7, 1964

Introduction

In 1922, Trautz and Winkler[1] initiated the study of the gas phase thermal rearrangement of cyclopropane. However, it was not until 1934 that Chambers and Kistiakowsky[2] carried out a quantitative study of this reaction. It has since been studied extensively for two reasons: 1) to test the unimolecular theories of Hinshelwood[3], Rice and Ramsperger[4], Kassel[5], and Slater[6]; and 2) to elucidate the mechanism of the reaction. This abstract is a critical review of the extensive studies on the mechanism of the gas phase thermal rearrangement of cyclopropane. References to the qualitative aspects of theoretical predictions are made where applicable.

Kistiakowsky's Mechanisms for the Rearrangement

Chambers and Kistiakowsky[2] found that the rate of the thermal rearrangement of cyclopropane was pressure dependent, being first order at sufficiently high pressures, and that the pattern of pressure dependence was as predicted by the Kassel theory of unimolecular reactions.[5] The rate, however, was independent of the surface/volume ratio, both in the high and low pressure regions. They concluded, therefore, that the reaction was a homogeneous, unimolecular one. Since no change of pressure was noticed during a run, it was supposed that very little, if any, side reactions such as polymerization or cracking occurred during the reaction. This was later confirmed by various workers with the use of v.p.c.[7,8,9] The high pressure rate constant between 470-520°C was found to be $k_\infty = 10^{15.17}\exp(-65{,}000/RT)\,\mathrm{sec}^{-1}$. The activation energy of 65 kcal./mole is very similar to the cracking of certain paraffins,[10] and this is suggestive that some similar mechanism might be operative in the thermal rearrangement of cyclopropane.[11] Hence they suggested the following mechanisms:



Mechanism 1 involves the rupture of C-C bond as the rate determining step, while mechanism 2 involves the migration of H as the rate determining step. The data they obtained could not distinguish between these two mechanisms. In the three decades that followed the proposal of these mechanisms, almost every experiment that might conceivably have differentiated them has been investigated.

A Qualitative Description of Two Unimolecular Reaction Theories

To review briefly, a unimolecular reaction is one in which the activated complex (the transition state) is formed from a single reactant molecule. Presumably the reactant molecules acquire the necessary energy through collision with other reactant or product molecules, or some added inert gas. When a molecule acquires an energy equal to or in excess of the activation energy, it is called an activated molecule. At sufficiently high pressures, an equilibrium will be established between reactant molecules and activated molecules. These activated molecules have a Maxwell-Botzmann energy distribution. The reason for such a distribution is that the reactant molecules themselves have such a distribution. Hence the rate determining step at high pressures is the decomposition of the activated molecules, and the reaction is first order. At sufficiently low pressures, the activated molecules no longer have a Maxwell-Boltzmann energy distribution, and the rate determining step becomes the rate of effective collision to form the activated molecules. The reaction thus becomes second order. The change from first order at high pressures to second order at low pressures gives rise to the pressure dependence of unimolecular reactions.[12] In practice, however, the second order rate may never be attained due to, among other things, wall activation as was found for cyclopropane.[13]

One of the most important features of Slater's theory on unimolecular reactions is that the rate is a function of n, the number of effective independent vibrational

modes[6b], that is, if there is a pair of degenerate modes, the contribution of the pair is, from his derivation of the rate equation, equivalent to one non-degenerate mode[6c]. The energy acquired by these n vibrational modes is forbidden to flow between themselves, that is, energy reshuffling during subsequent vibrations is not allowed. When the bond that possesses sufficient energy for bond breaking or the "critical co-ordinate" reaches sufficient extension, reaction is said to occur. For mechanism 1 where C-C bond breaking is the rate determining step, only the three skeletal carbons are involved, according to Slater, and n is 3.[7] For mechanism 2 where C-H bond breaking is the rate determining step, all nine atoms in cyclopropane are involved, and n is 14.[14] Thus, this theory could be used to distinguish between mechanisms 1 and 2.

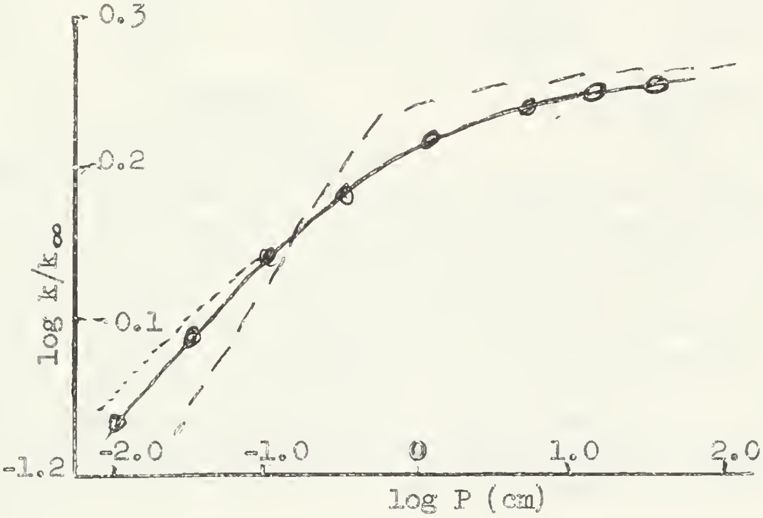
In contrast, the Kassel theory,[5] which is very similar to the Rice-Ramsperger theory,[4] allows free energy transfer in the activated molecule. The energy is said to be reshuffled by every vibration of the activated molecule. Such intramolecular energy transfer is rapid compared to the lifetime of the activated molecule. Eventually sufficient energy is localized, through such reshuffling, in a so-called "critical mode", and when that happens, reaction is said to occur. The more energy the activated molecules possess, the faster the energy finds its way to the "critical mode", or the faster the reaction. This theory, however, cannot distinguish between the two mechanisms.

Objections to Slater's Theory

The work of Trotman-Dickenson, et al.[15] gave Slater's theory its greatest triumph. They showed that a plot (Fig. 1) of $\log k/k_\infty$ vs $\log P$, (where k is the rate constant at a given pressure, k_∞ is the high pressure rate constant, and P is the pressure) calculated from Slater's theory (solid line) with n of 13 or 14 agrees exactly with the experimental points (circles) at 470°C. Kassel's plot (dotted line) deviates slightly from the experimental plot at low pressures, while Hinshelwood's plot (dashed line) does not fit at all. This gives strong support to mechanism 2. This agreement, though spectacular, is probably fortuitous as will be demonstrated below.

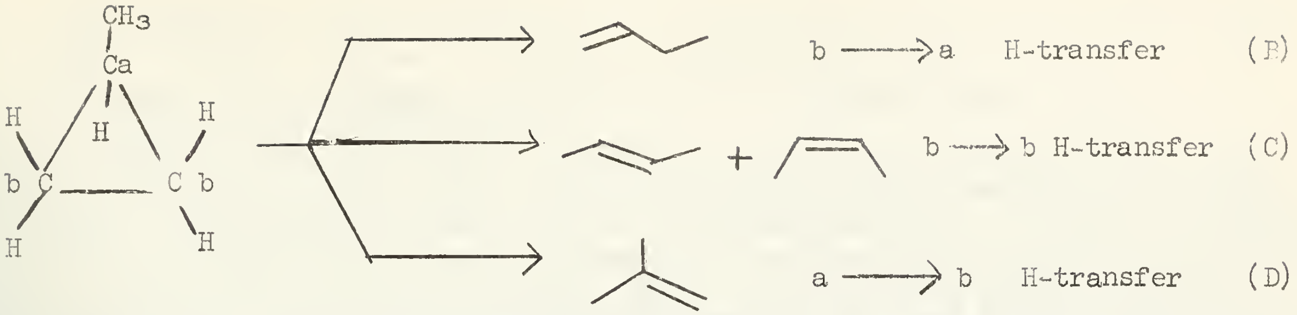
Fig. 1

The Pressure Dependence of the Structural Isomerization of Cyclopropane



__________Slater's, ...Kassel's, and _ _ _ _ _Hinshelwood's theoretical curves; oooooooo experimental curve.

Butler and Kistiakowsky[16] synthesized some "hot" methylcyclopropane by reacting methylene with a large excess of either cyclopropane or propene. The methylenes come from three different sources: irradiation of ketene at 2600 Å, the same at 3100 Å, and irradiation of diazomethane by polychromatic light. The methylcyclopropane produced by these reactions possesses energies of about 115 kcal/mole (Table I) which is about 50 kcal/mole higher than the activation energy needed for its isomerization (Table II). The isomerized product as analyzed by v.p.c. are 1-butene, cis and trans-2-butene, and isobutene, resulting from b to a H-transfer, b to b H-transfer, and a to b H-transfer respectively (Equations B - D).



They found that the yields of the various butenes were the same within experimental error regardless of the source of methylene, and whether cyclopropane or propene was employed for the synthesis of the "hot" methylcyclopropane (Table I). This finding is in direct contradiction to Slater's predictions. When a methylene is inserted between a C-H bond, as in its reaction with cyclopropane, it excites different vibrational modes than when it opens up a double bond, as in its reaction with propene. Hence the methylcyclopropane made by these two methods must, according to Slater's assumption of no intramolecular energy transfer, give different yields of the various butenes. Since this is not observed experimentally, Slater's theory cannot be correct.

Table I

Source and Energy of "Hot" Methylcyclopropane and the Relative Probabilities of Hydrogen Transfer

Source of "hot" methylcyclopropane	E kcal/mole	α_{ba}	α_{ab}	α_{bb}	$\frac{CB}{TB}$
Diazomethane and cyclopropane	122	1.19 ± 0.04	0.65 ± 0.02	0.98 ± 0.04	1.05 ± 0.21
Ketene (3100Å) and cyclopropane	119	1.01 ± 0.02	0.625 ± 0.06	1.17 ± 0.16	1.43 ± 0.45
Ketene (2600Å) and cyclopropane	117	0.95 ± 0.05	0.665 ± 0.045	1.21 ± 0.05	1.22 ± 0.35
Diazomethane and propene	115	0.90 ± 0.18	0.75 ± 0.15	1.10 ± 0.12	0.99 ± 0.17
Ketene (3100Å) and propene	111	1.32 ± 0.25	0.90 ± 0.20	1.13 ± 0.18	1.20 ± 0.22
Ketene (2600Å) and propene	109	1.53 ± 0.50	0.65 ± 0.15	1.10 ± 0.20	1.11 ± 0.26

$\alpha_{ba} = 2.5 \frac{\text{1-butene}}{\text{total butenes}}$; $\alpha_{ab} = 5 \frac{\text{isobutene}}{\text{total butene}}$; $\alpha_{bb} = 2.5 \frac{\text{cis and trans-2-butene}}{\text{total butene}}$;

CB and TB mean cis and trans-2-butene, respectively.

As pointed out earlier, n, the number of effective independent vibrational modes, is 14 for cyclopropane.[7] This value takes into account the seven doubly degenerate modes of cyclopropane. In the case of 1,2-dideuteriocyclopropane, there are no degenerate modes, and the value of n should be 21. This was not the case. It was found that in order for experimental data to agree with theoretical predictions, an n of 13 or 14 would have to be used for 1,2-dideuteriocyclopropane, just as cyclopropane itself. Slater's theory again fails to predict correctly.

In view of these rather serious failures of the Slater theory, one should, at least, discard it as a guide in differentiating between the two mechanisms proposed by Kistiakowsky. It should be pointed out here that the objections against Slater's theory do not apply to Kassel's theory.

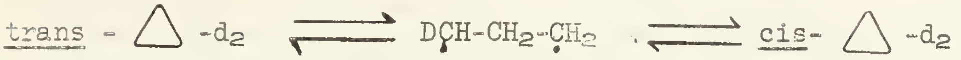
Experiments to Differentiate Kistiakowsky's Mechanisms

It has been found that 1,2-dideuteriocyclopropane undergoes thermal structural isomerization as well as geometric isomerization.[7,17] The activation energy for structural isomerization was found to be about 2 kcal/mole higher than that for geometric isomerization, or the rate of geometric isomerization is about 12 times faster. It was also found that the rate of geometric isomerization is about 16 times faster than that for structural isomerization for "hot" 1,2-dideuteriocyclopropane prepared from reaction of methylene with trans-1,2-dideuterioethene.[18] Hence it seems reasonable to assume that geometric and structural isomerization proceed through a similar mechanism. Consequently, any arguments derived from geometric isomerization will be considered applicable to structural isomerization, as has been suggested by a number of workers.[17,18,19,20]

Rabinovitch, et al.,[17] proposed three possible mechanisms for the geometric isomerization of 1,2-dideuteriocyclopropane.

i. Ring rupture forming a trimethylene diradical and reversible recyclization as,

e.g.



$$\underline{\text{trans}} - \triangle - d_2 \rightleftharpoons D\underset{\bullet}{C}H\text{-}CH_2\text{-}\underset{\bullet}{C}H_2 \rightleftharpoons \underline{\text{cis}} - \triangle - d_2$$

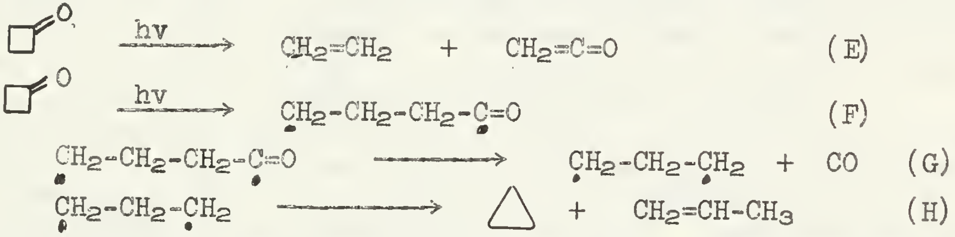
ii. Intermolecular exchange, either radical or non-radical; and

iii. Intramolecular H(D)-migration.

Mechanisms (ii) and (iii) are readily eliminated because they would give rise to asymmetrical deuteriocyclopropanes which were not present as determined by I.R. and mass spectrometry. Mechanism (i) seems to be the only reasonable one. It should be pointed out that the trimethylene diradical intermediate drawn for mechanism (i) is probably not a very accurate description of the actual species. Rabinovitch, et al.,[7] prefers the term "expanded ring" intermediate because the open ends are not free of each other's sphere of influence. The terms trimethylene diradical and "expanded ring" will be used interchangeably in this abstract.

The existence of the trimethylene diradical or "expanded ring" intermediate has been questioned because of failure to trap it by scavengers such as oxygen,[7] nitric oxide,[9] and ethene.[21] Benson[19,22] calculated that the life time for the trimethylene diradical at 444°C is $10^{-10.5}$ seconds. This is at least 100 fold less than collision times at 1 atmosphere, and as such it cannot be trapped. Seubold[23] gave a qualitative argument by pointing out that even the recombination of methyl radicals is about 1,000 times faster than their reaction with nitric oxide. Rabinovitch, et al.,[17] calculated the relative density of energy levels over a range of relevant (around 60 kcal/mole) energies for cyclopropane and trimethylene diradical, and showed that recyclization of trimethylene diradical is too fast to permit trapping them.

Frey and co-workers[21] found that the photolysis of cyclobutanone at 100° and 25 mm Hg pressure gives ethene, ketene, carbon monoxide, cyclopropane, and propene. In the presence of very large excess (500 mm Hg) of ethene, they found, in addition to the above products, about 8% of C_5 olefins. The following pathways were proposed to explain their observations:



$$\xrightarrow{hv} CH_2{=}CH_2 + CH_2{=}C{=}O \qquad (E)$$

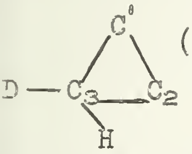
$$\xrightarrow{hv} \underset{\bullet}{C}H_2\text{-}CH_2\text{-}CH_2\text{-}\underset{\bullet}{C}{=}O \qquad (F)$$

$$\underset{\bullet}{C}H_2\text{-}CH_2\text{-}CH_2\text{-}\underset{\bullet}{C}{=}O \longrightarrow \underset{\bullet}{C}H_2\text{-}CH_2\text{-}\underset{\bullet}{C}H_2 + CO \qquad (G)$$

$$\underset{\bullet}{C}H_2\text{-}CH_2\text{-}\underset{\bullet}{C}H_2 \longrightarrow \triangle + CH_2{=}CH\text{-}CH_3 \qquad (H)$$

They felt that the C_5 olefins came from the reaction of trimethylene diradical (Equation G) with ethene. Since they were unable to trap the trimethylene diradical in the thermal rearrangement of cyclopropane with ethene, they felt that it could not be an intermediate. It seems that the reaction of ethene and acyl radical (Equation F) to give C_5 olefins and carbon monoxide; a concerted cyclization or hydrogen transfer of the acyl radical to give cyclopropane and carbon monoxide, and propene and carbon monoxide respectively, and/or reaction of methylene, produced from the irradiation of ketene, with ethene could also account for the observed results. Furthermore, the trimethylene diradical that might have been produced might not be the same species as the trimethylene diradical ("expanded ring") produced in the thermal rearrangement of cyclopropane. Hence one must consider Frey's results as, at a minimum, inconclusive, and that the trimethylene diradical is still a reasonable postulate.

F. T. Smith[24] proposed an alternate explanation for the cis-trans isomerization of 1,2-dideuteriocyclopropane. He suggested a transition state like (I), where all five atoms are co-planar, and the H is partially bonded to the adjacent carbon. This requires twisting D-C-H to be in the same plane as the other carbons. The two hydrogens initially bonded to C_2 will remain out of plane. When the D-C-H returns to the ground state configuration, geometric isomerization could occur. Such a process would not give asymmetric dideuteriocyclopropane, which is in agreement with experiment. A complete transfer of H (or D) would result in structural isomerization, and is a mechanism similar to mechanism 2 (Equation A). Some rather serious objections could be raised against this mechanism.

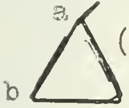


(I)

The high pressure (first order region) geometric isomerization of cis-1,2-dimethylcyclopropane between 380-420°C had a $k_\infty = 10^{15.25}\exp(-59{,}4200/RT)$ sec.$^{-1}$,[9] and that of

cis-1,2,3-trimethylcyclopropane between 395-450°C had a $k_\infty = 10^{15.78}\exp(-60,950/RT)$. $sec.^{-1}$ [25] The activation energies are the same within experimental error. But the geometric isomerization of trans-1,2-dideuteriocyclopropane at high pressures between 414-474°C had a $k_\infty = 10^{16.0}\exp(64,2000/RT)\ sec.^{-1}$ [17] The activation energy of this reaction is about 4 kcal/mole higher than that for 1,2-dimethylcyclopropane or 1,2,3-trimethylcyclopropane. From steric effects, one would expect, according to the F.T. Smith mechanism, that the twisting of the more bulky $\overset{CH_3}{\underset{H}{C}}$ groups would have a higher activation energy than $\overset{D}{\underset{H}{C}}$, which is contrary to experimental observations. The discrepency can be explained by the trimethylene diradical mechanism since it is known that C-C bond is weakened by substitution.[26] This explanation is further supported by the observed $k_\infty = 10^{15.08}\exp(-58,870/RT)\ sec.^{-1}$ [27] for the geometric isomerization of cis-1-ethyl-2-methylcyclopropane between 396-446°C.

From product ratios, Chesick[8] found that in the thermal rearrangement of methylcyclopropane, the energy required for breaking the C_a-C_b bond (see J) is about 2.3 kcal/mole less than that for breaking the C_b-C_b bond. Kistiakowsky found the same difference in his work with "hot" methylcyclopropane.[16] He seems to think that this difference in activation energy could be explained simply by the F.T. Smith mechanism because for a C_b-C_b bond breaking a group with a large moment of inertia, $\overset{CH_3}{\underset{H}{C}}$, must be rotated instead of CH_2. It is difficult to see how the moment of inertia is related to activation energy. This 2-3 kcal/mole difference could easily be explained by the fact that carbon-carbon bond is weakened by substitution of other groups[26] if the C-C bond rupture is important.



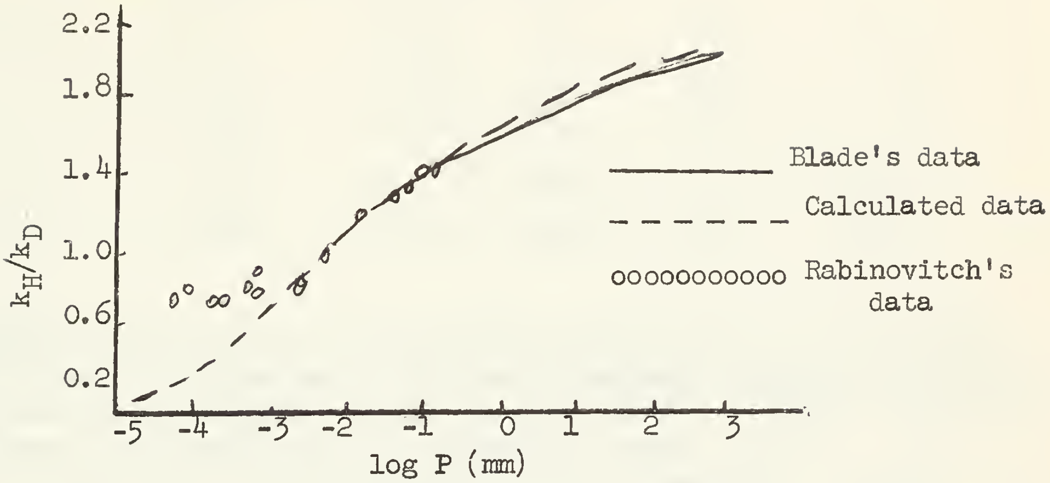
(J)

For 1,1-dimethylcyclopropane, the high pressure structural isomerization is $k_\infty = 10^{15.05}\exp(-62,600/RT)\ sec.^{-1}$ between 447-511°C.[28] It gives equal amounts of 3-methylbutene-1, and 3-methylbutene-2 in quantitative yields. From the similarities in the pre-exponentials, and the activation energies of this and the other alkyl substituted cyclopropanes discussed so far, it seems reasonable to assume that the methyl groups do not migrate and that the methyl hydrogens do not participate directly in the isomerization. Hence the results obtained from the substituted cyclopropanes discussed so far can reasonably be assumed to be applicable to cyclopropane itself.

The first efforts to study hydrogen isotope effect on the thermal rearrangement of cyclopropane were made by Lindquist and Rollefson,[29] and Weston.[30] They worked with monotritiated cyclopropane, but due to difficulties in radioactive counting, their results were not reliable enough to be meaningful. Blades[31] found that the isotope effect for cyclopropane-d_6 is $k_H/k_D = 0.82\exp(1300/RT)$ at 60 cm Hg pressure and temperatures between 407-514°C. This isotope effect is pressure dependent. The isotope effect at 445°C is 2.04, which compares favorably with a value of 2.5 at 466°C for the radical hydrogen abstraction of acteone and acetone-d_6,[32] and a value of 3.0 for the hydrogen dissociation of chloroform and deuteriochloroform at 245°C.[33] This agreement suggests that the observed isotope effect for cyclopropane-d_6 is probably primary. This is confirmed by its excellent agreement with $k_H/k_D = 0.88\exp(1300/RT)$ at high pressures[34] which was the theoretically calculated value for primary isotope effect for cyclopropane. A plot of k_H/k_D vs log P (Fig. II) also shows good agreement between calculated and experimental values.[35] The disagreement between calculated and observed values at pressures below 10^{-2} mm might be attributed to wall-activated reactions.[13] This certainly lends strong support for mechanism 2 (Equation A), but we should not discard mechanism 1 on this evidence alone. In addition, Simmons and Rabinovitch found only a secondary isotope effect for the geometric isomerization of cis-1,2-dimethylcyclopropane-d_8.[36]

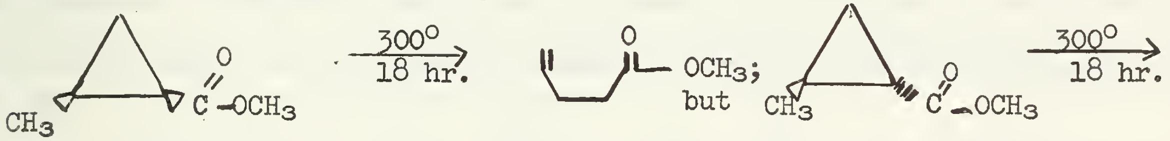
Fig. II

Pressure Dependence of Isotope Effect



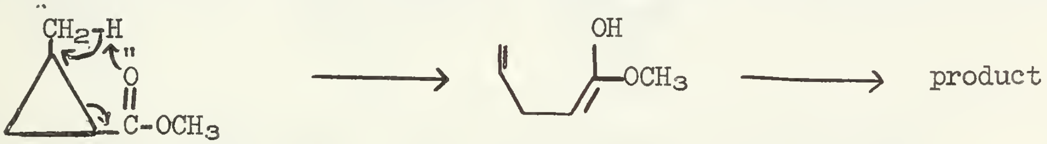
The pyrolyses of other substituted cyclopropanes have been studied. But they seem to go by entirely different mechanisms and are not illuminating to the mechanism of the thermal rearrangement of cyclopropane. Briefly, here are some examples:

McGreer[37] found the following:


O
CH3
C -OCH3
300°
18 hr.
O
OCH3;
but
O
CH3
C -OCH3
300°
18 hr.
N.R.

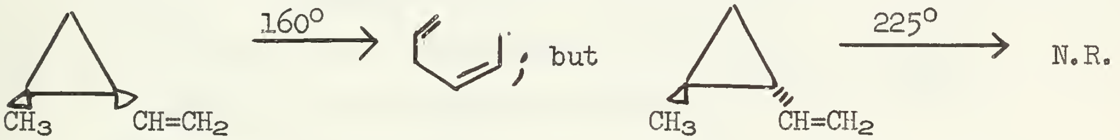
(K)

The stereoselectivity can formally be explained by the following mechanism:


CH2-H
O
C-OCH3
OH
OCH3
product

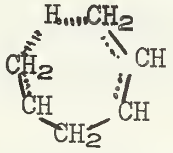
(L)

Ellis and Frey[38] also found the following reaction to be stereoselective:


160°
CH3
CH=CH2
; but
225°
CH3
CH=CH2
N.R.

(M)

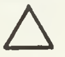
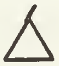
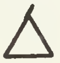
This can be explained formally by a cyclic transition state as follows:

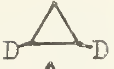
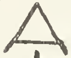
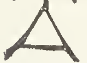
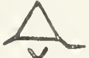
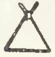
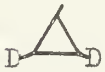

H
CH2
CH2
CH
CH
CH
CH2

(N)

Table II

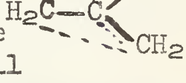
Summary of High Pressure (First Order) Rate Parameters

Author	Ref.	Temp. Range	Compd.	log A		E_a kcal/mole	
				Geom.	Struct.	Geom.	Struct.
Kistia-kowsky	2	470-520°C		-----	15.17	-----	65.0
Chesick	8	440-490		-----	15.04	-----	65.0
Rabino-vitch	39	380-420		-----	14.61	-----	62.4

Author	Ref.	Temp. Range	Compd.	log. A Geom.	 Struct.	E_a kcal/mole Geom.	 Struct.
Rabino-vitch	17	414-474		16.01	15.2	64.2	65.5
Frey	9	380-420		15.25	-----	59.4	-----
Frey	25	395-450		15.78	-----	61.0	-----
Frey	27	396-446		15.08	-----	58.9	-----
Frey	28	447-511		-----	15.05	-----	62.6
Rabino-vitch	39	380-420		15.35	14.43	60.5	62.3

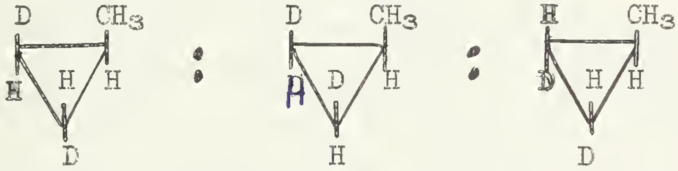
Rabinovitch's Mechanism

From all the work on the mechanism of the thermal rearrangement of cyclopropane considered thus far, it seems that no one of the two mechanisms originally proposed by Kistiakowsky can satisfactorily explain all the observed facts. In 1961, Rabinovitch, et al.[37], first suggested the possibility of a transition state like (O), or in other words a concerted process involving both of Kistiakowsky's mechanisms. In 1964, Rabinovitch, et al.,[34] first obtained quantitative data in support of this concerted mechanism, which is consistent with all the experimental data obtained to date.



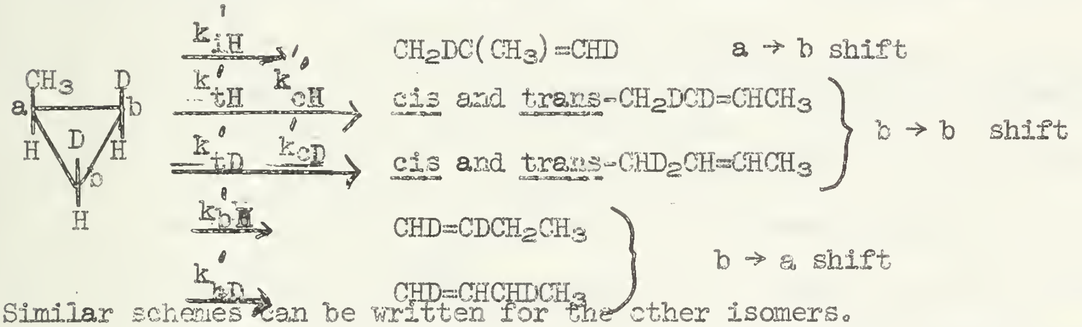
(O)

Rabinovitch, et al.,[39] studied the thermal rearrangement of 1,2-dideuterio-3-methylcyclopropane. They found that geometric isomerization is much faster than structural isomerization, and that an equilibrium mixture of the deuterated methyl-cyclopropanes is attained before any substantial amount of structural isomerization has occurred. The equilibrium has the following ratio:



= 2:1:1

The structural isomerization can be illustrated by the scheme:



(P)
(Q)
(R)
(S)
(T)

Similar schemes can be written for the other isomers.

The individual rate parameters for the reaction scheme are summarized in Table III.

Table III

Experimental Rate Parameters for Methylcyclopropane Isomerization

Rate Const.	k/k'	methylcyclopropane log A	 E_a kcal/mole	methylcyclopropane-d_2 log A	 E_a kcal/mole
k_s	1.36±0.03	14.61±0.19	62.4±0.6	14.43±0.16	62.3±0.5
k_i (a → b)	1.10±0.03	14.06±0.21	64.3±0.6	13.98±0.15	64.1±0.5
k_t (b → b)	1.30±0.04	14.32±0.19	64.4±0.6	14.26±0.13	64.5±0.6
k_c (b → b)	1.28±0.03	13.97±0.17	61.9±0.6	13.76±0.15	61.5±0.5
k_b (b → c)	1.50±0.03	14.14±0.18	62.0±0.6	13.87±0.16	61.6±0.5

The ratio k_i/k'_i = 1.10±0.03 is the rate ratio for the formation of isobutene from methylcyclopropane and 1,2-dideuterio-3-methylcyclopropane respectively. This is the first measured secondary isotope effect for the structural isomerization of cyclopropane. If this order of magnitude is assumed to be correct for the corresponding ratio for the formation of other deuteriobutenes by H migration, ~~and~~ one obtains, by appropriate calculations, k_{tH}/k'_{tD} = 1.59 and k_{cH}/k'_{cD} = 1.41 or an average of 1.50, and k_{bH}/k'_{bD} = 2.36. These isotope effects compare favorably with k_H/k_D = 2.18 and 1.96 for 1,2-dideuteriocyclopropane[7] and cyclopropane-d_6[31] respectively and are therefore primary. This reflects that the breaking of the C-D bond plays an important role in the transition state. In addition, from product ratios, it was found that the formation of isobutene, i.e. the breaking of C_t-C_b bond, has an activation energy of about 2.3 kcal/mole higher then for butene-2 as was found by Chesick[8]. This shows that the rupture of a particular C-C bond is important in the formation of the transition state. Since it is known that methyl substitution lowers C-C bond energies,[26] mechanism 1 (Equation A) should be responsible for these effects. It may therefore be concluded that the mechanism for the thermal rearrangement of cyclopropane, from the best evidence available, is a concerted combination of mechanisms 1 and 2.

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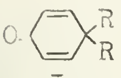
SOME RECENT STUDIES OF THE PHOTOCHEMISTRY OF CROSS-CONJUGATED CYCLOHEXADIENONES

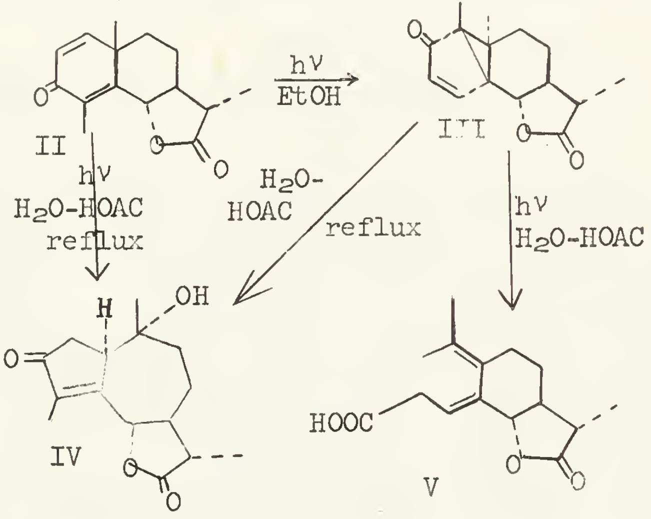
Reported by Elizabeth McLeister

December 10, 1964

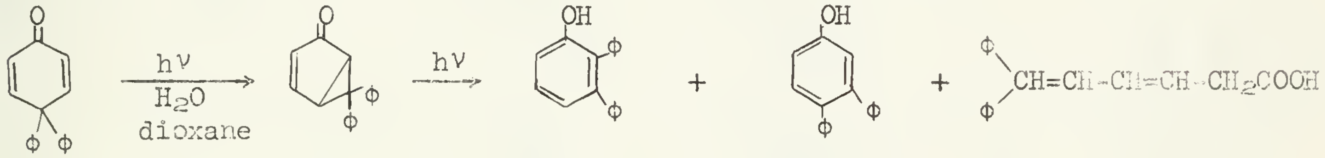
Rearrangements of cross-conjugated cyclohexadienones (I) under the influence of ultraviolet light have been the subject of much study and interest during the past few years. One of the first systems to be studied was that of santonin (II) and its photoproducts. The conversions of santonin to lumisantonin (III), isophotosantonic lactone (IV), and photosantonic acid (V) are summarized in the following diagram:[1,2,3] Formation of III and IV is stereospecific; the structures of these products have been confirmed by X-ray analysis of bromo derivatives, that of lumisantonin only recently.[4] Photoproducts analogous to III (referred to as "lumi" products) have been formed from a number of santonin-like and steroidal dienones, with phenols sometimes being formed as additional products of steroidal dienones.[1,2]



I

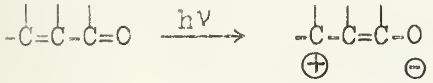


Zimmerman has reported that 4,4-diphenylcyclohexadienone (VI) forms the bicyclic product VII upon irradiation in aqueous dioxane. Further irradiation of VII gives two phenols (VIII and IX) and an acid (X).[5,6]



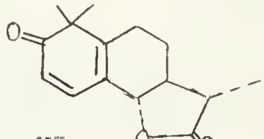
VI VII VIII IX X

Upon observing that such skeletal rearrangements are similar to those which occur in electron-deficient systems in "ground-state" chemistry, Chapman has proposed that photochemical excitation leads, by an unspecified process, to a dipolar intermediate (a), which can rearrange to give the observed products:[2]



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O \xrightarrow{h\nu} -\underset{\oplus}{\overset{|}{C}}-\overset{|}{C}=\overset{|}{C}-\underset{\ominus}{O}$$

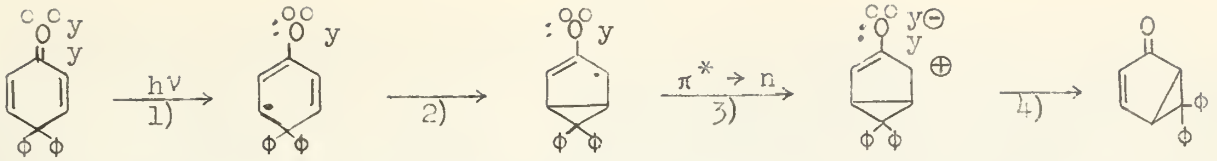
a



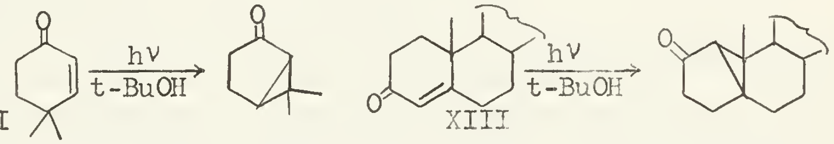
XI

Such a treatment predicts the formation of XI upon irradiation of lumisantonin, and XI has since been isolated as an intermediate in the conversion of III to V.[7,8]

Because many of the transformations of dienones have resulted from irradiation through Pyrex, which cuts out light of wave lengths below 300 mμ, Zimmerman has concluded that such reactions are the result of $n \rightarrow \pi^*$ excitation. Such excitation, he continues, would result in increased electron density delocalized over the π system, leaving the oxygen somewhat positively charged; yet he concedes that the rearrangements are those typical of electron-deficient systems. Zimmerman has thus proposed the following scheme, illustrated for the formation of VII from VI: 1) An electron from a lone pair on carbonyl oxygen is excited to a π^* orbital and is delocalized over the ring. 2) The excited species undergoes bond alteration (bond formation or breaking). 3) $\pi^* \rightarrow n$ demotion occurs, leaving the system electron-deficient. 4) The system rearranges to the observed product. Similar processes have been invoked to account for the formation of phenols and acid upon the further irradiation of VII.[5,6]

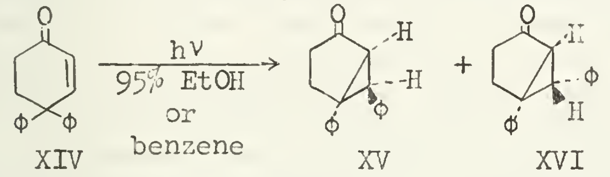


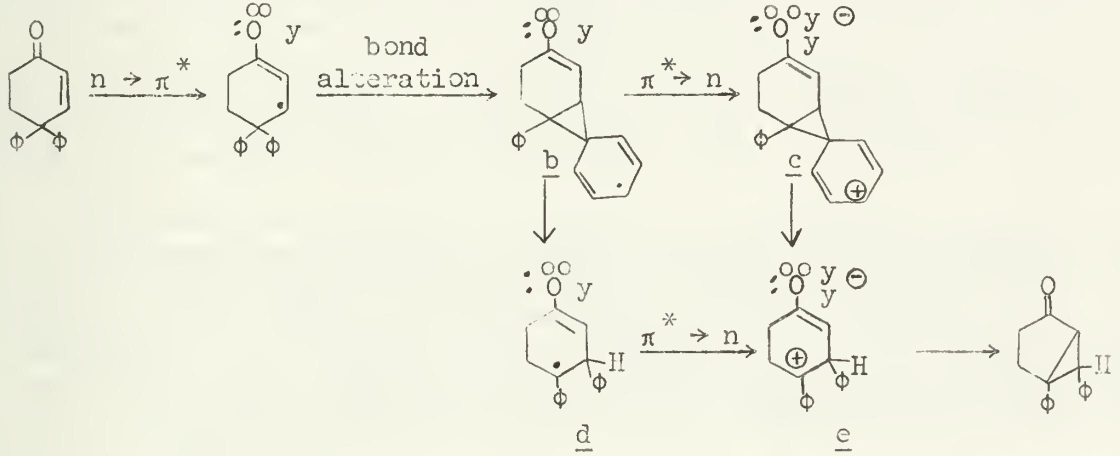
Several groups of workers have reported the photochemical formation of "lumi" products from the simple α,β-unsaturated ketones 4,4-dimethyl-2-cyclohexenone (XII) and Δ^4-cholestenone (XIII). On the basis of these results, it has been suggested that the first rebonding step of the Zimmerman hypothesis is not a necessary feature of these reactions of dienones.[2,9]

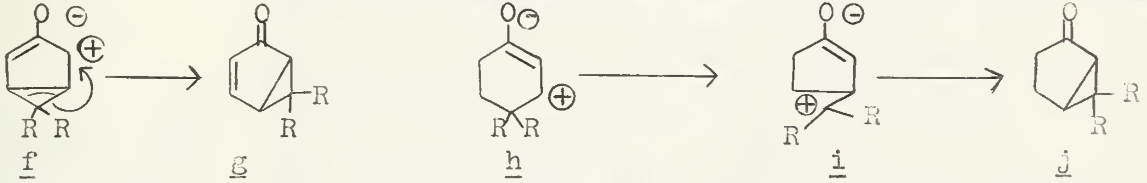


The studies described above have been reviewed in the references indicated.

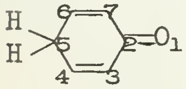
Zimmerman has recently studied the behavior of XIV upon irradiation through Pyrex in benzene or 95% ethanol.[10] The two products, which are photochemically interconvertible stereoisomers, have been assigned the structures XV and XVI. The formation of these products has been explained by the four-step process involving $n \rightarrow \pi^*$ excitation, bond alteration, $\pi^* \rightarrow n$ demotion, and subsequent ground-state rearrangements. The rebonding step proposed in this case is phenyl migration rather than the 3,5-bridging proposed for VI. The process may proceed with migration being completed before $\pi^* \rightarrow n$ demotion occurs (b→d→e), or after demotion (b→c→e). Zimmerman has suggested that C-4 migration (f→g) involving a second double bond is more efficient than phenyl migration (b→e), since the latter is observed only when the second double bond is absent. When phenyl migration cannot occur and a second double bond is absent, C-4 migration again becomes important, as in the case of 4,4-dimethyl-2-cyclohexenone. Zimmerman has illustrated a scheme for the rearrangement of the latter compound, for which Chapman has proposed the process (h→i→j).[2]



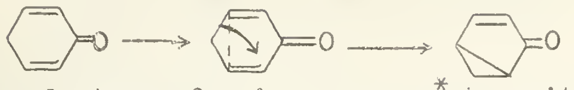


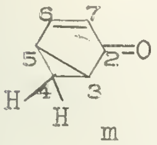


Hoffmann, in studies not yet published, has presented an alternative explanation of how rearrangements resembling those of electron-deficient systems may occur as a result of $n \rightarrow \pi^*$ excitation.[11] Using extended Hückel calculations, he has calculated charge distributions and overlap populations for the ground state and the $n \rightarrow \pi^*$ excited state of the imaginary cyclohexadienone molecule k. From these studies he has concluded that the lone pair of electrons on oxygen is extensively delocalized in the ground state, and that $n \rightarrow \pi^*$ excitation produces relative electron deficiency at O, C_3, C_7, and C_5, and relative electron excess at C_2, C_4, and C_6. (This charge distribution is contrary to that proposed by Chapman.) The C_4-C_6 overlap population becomes slightly less negative, indicating a slight bonding tendency. The formation of the "lumi" product can



be visualized as follows, the dotted line indicating bonding tendency and the arrow representing bond migration. Similar calculations indicate that two different excited states may be involved in the photolysis of the "lumi" product m. One is an n → π* transition which weakens the C_2-C_3 bond and can lead to the 3,5-hexadienoic acid (X) formed by the photolysis of VII. The second state involves a transition to a π* orbital from a σ orbital of the cyclopropane ring accompanied by weakening of the C_3-C_5 bond and electron deficiency at C_3 and C_5, producing the two phenols VIII and IX.





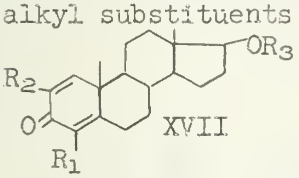
m

In a recent communication, Richards has described some photosensitization studies carried out on santonin and lumisantonin.[8] Irradiation of santonin and benzophenone in a solution in which benzophenone (E_T = 68.5 kcal/mole) absorbed 95% of the incident radiation (3660 Å), converted santonin to lumisantonin at a rate 1.7 times as great as that observed for a similar solution of santonin alone. Michler's ketone (E_T = 61.0 kcal/mole) did not sensitize the reaction. Irradiation of santonin in piperylene completely quenched the conversion of II to III, although the singlet energy of piperylene (2300 Å) is far above that of the incident radiation. From these results it was concluded that excitation of santonin produces a singlet state, which undergoes intersystem crossing to a triplet state, which then rearranges to lumisantonin. Similar experiments indicated the transfer of triplet character and energy from photosensitizers such as Michler's ketone to lumisantonin.

Zimmerman has proposed that the photoisomerization of 4,4-diphenylcyclohexadienone (VI) also may proceed via a triplet state intermediate.[12] In an experiment similar to that described by Richards, it was found that with acetophenone (E_T - 73.9 kcal/mole) present in concentration to absorb 98% of the incident light, VI was converted to VII four times as fast as the dienone alone. Since the same product resulted as in the unsensitized reaction, it was assumed that the dienone triplet is an intermediate in the unsensitized reaction. The reaction was not quenched by naphthalene, which has a triplet state energy of 61 kcal/mole, while that of the dienone is 68.8 kcal/mole; however, it was proposed that the dienone triplet rearranges too rapidly for quenching to occur.

As Hammond has pointed out, one cannot completely eliminate the possiblity that the transformations occurring in a photochemically excited state may bear little resemblance to processes occurring in "ground state" chemistry.[9] The possibility that an electronically excited state may undergo adiabatic radiationless transition to a vibrationally excited ground state, which may be the actual species undergoing rearrangement, has been considered by Zimmerman; however, he has concluded that in solution such a vibrationally excited molecule would quickly lose its excess energy by collision with other molecules.[10]

Effect of alkyl substituents: Several groups of workers have studied the effects of alkyl substituents upon the photochemical transformations of cross-conjugated dienones. Irradiation of 4-methyl-1-dehydrotestosterone (XVIIa) and the 2,4-dimethyl analogue (XVIIb) in dioxane with a high-pressure mercury vapor lamp through quartz, gave high yields of the respective "lumi" products.[13] In contrast, irradiation of the unsubstituted dienone XVIIc under identical conditions gave a complex mixture of five ketones (A_1-A_5) and four phenols (B_1-B_4).[14] Orientation experiments, in which pure samples of the various ketonic products were irradiated under the previous reaction conditions, gave the information summarized in the following diagram, which also illustrates the structures assigned to the various products shown on the following page. (Ketone A_5 was not identified.) It should be emphasized that these experiments, carried out on individual compounds, do not necessarily represent what takes place in the complex irradiation of XVIIc, nor do they indicate that the conversions occur only via the indicated products as intermediates.

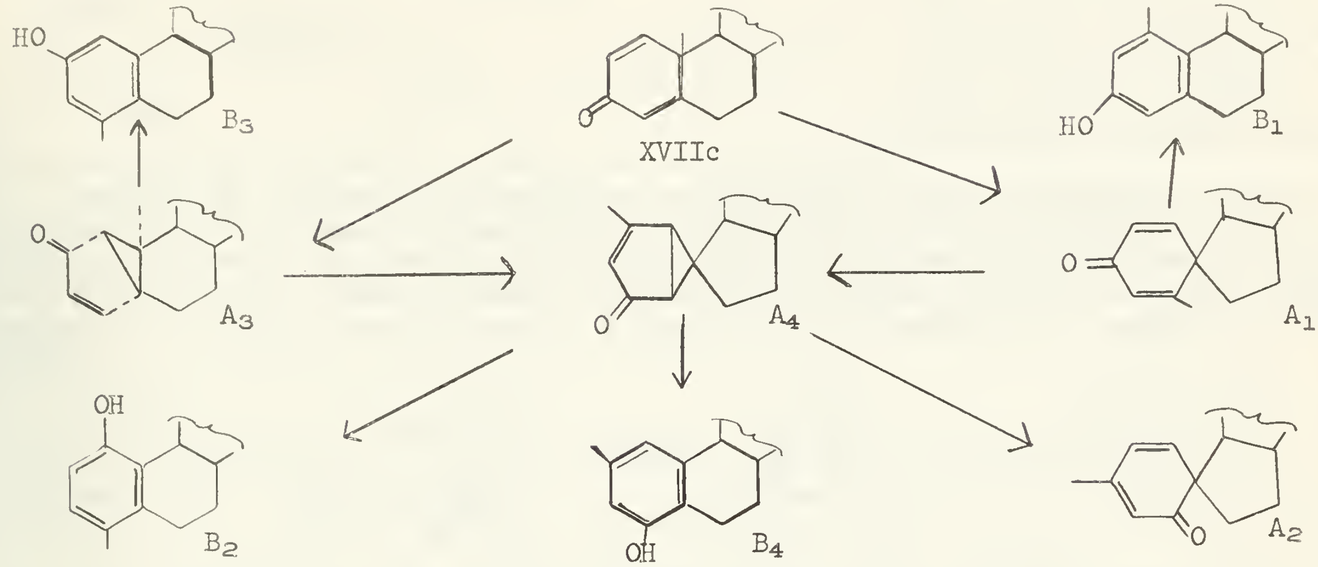


XVII

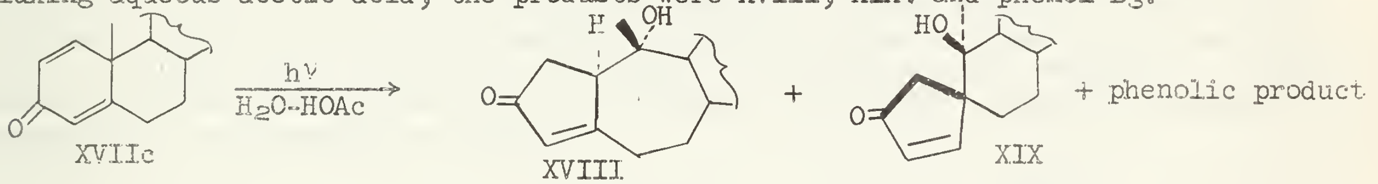
a R_1=CH_3, R_2=R_3=H
b R_1=R_2=CH_3, R_3=H
c R_1=R_2=H, R_3=Ac
d R_2=CH_3, R_1=R_3=H

Irradiation of XVIIc in dioxane with a low pressure mercury vapor lamp (emitting 95% of its radiation at 2537 Å) gave the "lumi" product A_3 in 62% yield, with only traces of B_1 and B_2. The formation and apparent stability of "lumi" product upon irradiation with a low pressure lamp in non-aqueous media has been observed with other

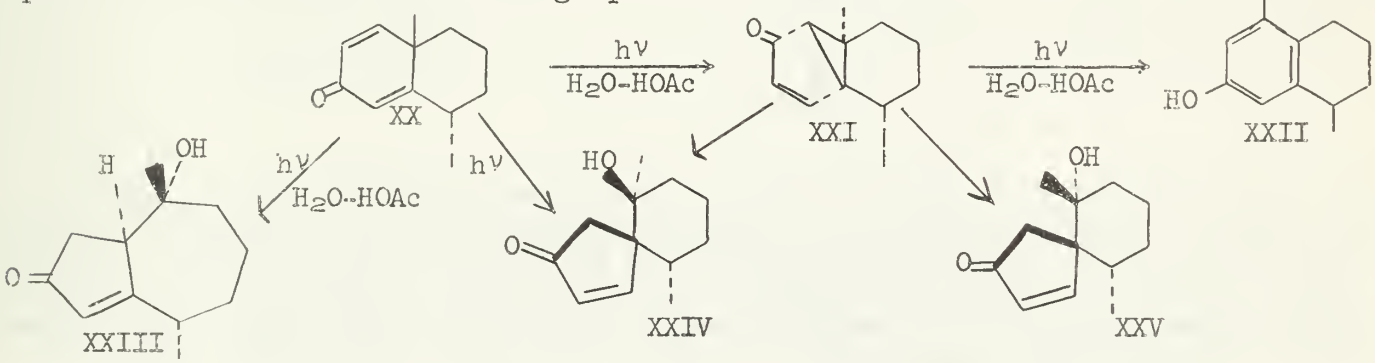
dienones[15] and is not understood; it has, however, proved useful for the preparation of high yields of "lumi" products.



Upon irradiation in 45% acetic acid at room temperature, with a high pressure mercury vapor lamp and a Vycor filter (cutting off most light of wave lengths below 220mμ), dienone XVIIc gave the hydroxy ketone XVIII, analogous to isophotosantonic lactone formed under similar conditions, the spiro ketone XIX, and the phenol B_1.[16] In refluxing aqueous acetic acid, the products were XVIII, XIX, and phenol B_3.[16,17]



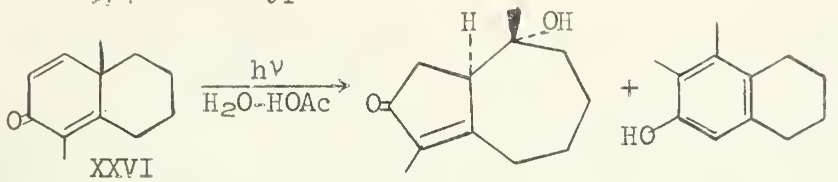
More extensive studies were carried out upon the model dienone XX.[16] Irradiation in aqueous acetic acid (high pressure lamp, Vycor filter) at room temperature gave the 5/7 fused ketone XXIII, the spiro ketone XXIV, and the phenol XXII. If the irradiation was interrupted before all of XX could be consumed, the "lumi" product XXI could be isolated; however, none of this material was present at the end of the reaction. Photolysis of XXI at room temperature in aqueous acid gave the phenol XXII; refluxing XXI in the same solvent gave XXIV and a small amount of a ketone believed to be epimeric to XXIV at the hydroxyl-bearing carbon (XXV). Small amounts of XXV were formed also upon irradiation of XX in refluxing aqueous acetic acid.



One surprising feature of this study is the formation of the spiro ketones XIX and XXIV, products not previously observed in the photolysis of dienones. The second unexpected result is that refluxing aqueous acid does not convert the "lumi" product to the azulenic ketone (XXIII), in contrast to the behavior of lumisantonin.

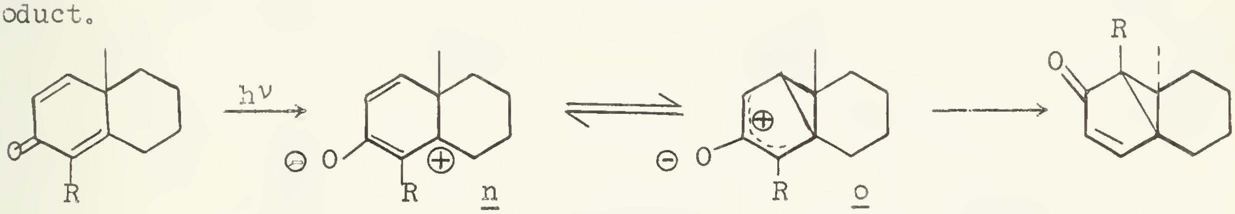
It has been concluded that the formation of the spiro compound is due to the absence of the 4-methyl group, since the only ketonic products formed upon irradiation in aqueous acid of 4-methyl-1-dehydrotestosterone (XVIIa)[13] and the model dienone XXVI are

of the 5/7 fused type.[18,19] The absence of the lactone ring of santonin appears to have little effect upon the primary ketonic products of the dienones, although it may account for the formation of phenols instead of acyclic unsaturated carboxylic acids. This possibility will be discussed later in the abstract.

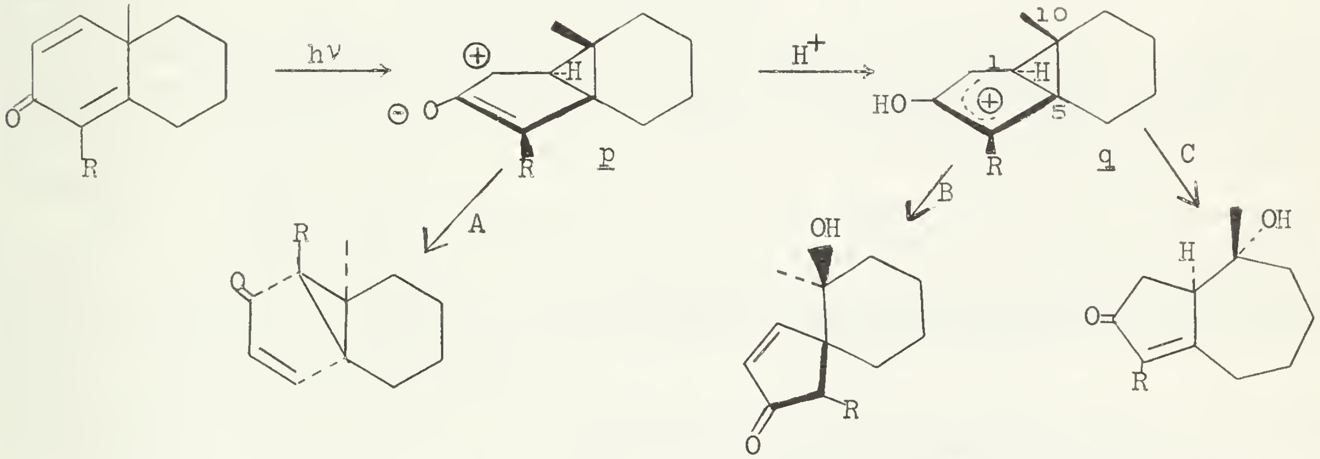


XXVI

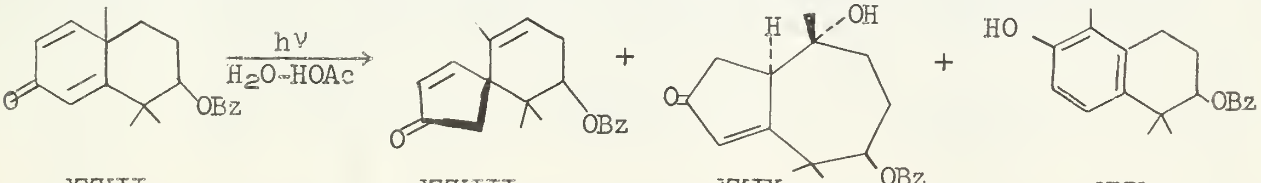
Chapman has proposed an explanation for the 4-alkyl effect, employing dipolar intermediates.[2] If species n and o are in equilibrium and not contributing forms of a resonance hybrid, the presence of a 4-alkyl group should stabilize the positive charge of o relative to n. Since o could be visualized as leading directly to "lumi" product while n could lead to other products, a 4-methyl group should favor formation of "lumi" product.



Since both XXIII and XXIV can be formed from XX with no observed intervention of the "lumi" compound, Kropp has proposed that photochemical excitation of a dienone gives the species p.[16] Such a structure would be in agreement with either the Chapman or the Zimmerman theories. In acidic media, p could be protonated to the cation q. Nucleophilic attack of water from the top of the molecule, accompanied by cleavage of the C_1-C_{10} cyclopropyl bond (steroid numbering system), followed by proton loss, could give the β-hydroxy spiro ketone (path B). Similarly, attack of water from the under side of the molecule, accompanied by breakage of the C_5-C_{10} bond could lead to the α-hydroxy 5/7 fused ketone (path C). The presence of the methyl group at C-4 may be responsible for predominance of path C.



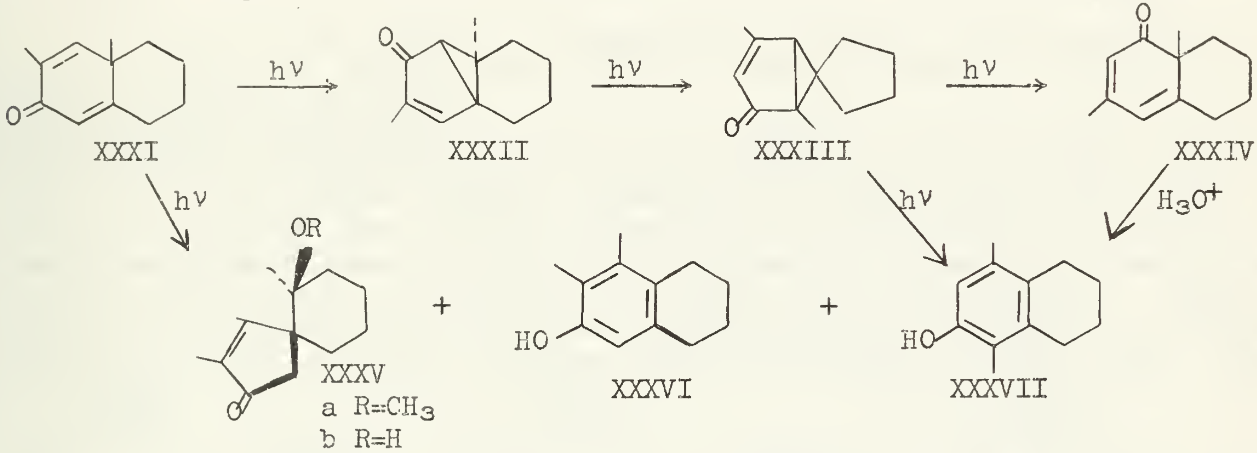
Kropp proposed that the 4-methyl effect might be steric in origin, involving hindrance to solvation of the intermediate q from the top of the molecule.[20] Such a process, he suggested, might be duplicated by a 6β-methyl substituent. To test this hypothesis, the 6,6-dimethyl dienone XXVII was irradiated in aqueous acid (high pressure mercury vapor lamp, Vycor filter); the products obtained were the spiro ketone XXVIII, the 5/7 ketone XXIX, and the phenol XXX. The 6β-methyl group appears to have affected sterically the path B process, resulting in proton loss instead of attack by water;



XXVII XXVIII XXIX XXX

however, appearance of significant amounts of a spiro ketone indicates that the 4-methyl effect, which leads to 5/7 fused ketones, probably is not steric in nature.

In an attempt to learn more about the effect of alkyl substituents, the irradiation of the 2-methyl-1,4-dien-3-one XXXI was studied in both neutral and acidic media.[15] Upon irradiation with a high pressure lamp through Vycor, dienone XXXI in methanol gave the linearly-conjugated dienone XXXIV as the principal product, with smaller amounts of XXXVa, XXXVI, and XXXVII. By interrupting the photolysis, or by irradiating with a low pressure mercury vapor lamp, it was possible to isolate intermediates XXXII and XXXIII. Sequence studies indicate that the order of formation of products is that shown in the diagram. A sequence of products analogous to XXXI through XXXIV appears to form upon the irradiation of 2-methyl-1-dehydrotestosterone (XVIId) in dioxane (high pressure mercury vapor lamp, through quartz), although the products have not yet been completely characterized.[21]

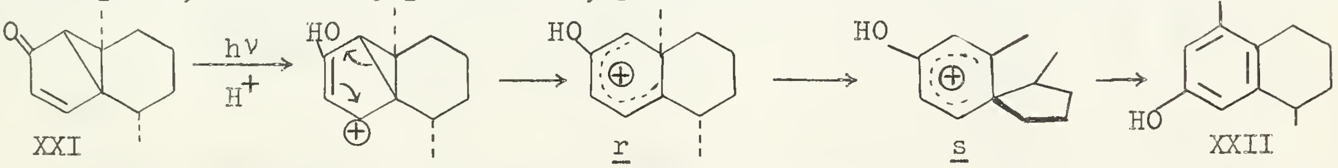


In 45% acetic acid, the principal photoproduct of XXXI is the spiro ketone XXXVb, along with smaller amounts of the phenols and traces of the ketones formed in the irradiation in methanol. Phenol XXXVII was found to form upon treatment of XXXIV with aqueous acid, or upon irradiation of XXXIII.[15]

It can thus be generalized that, upon irradiation in aqueous acid, 4-methyl dienones give predominantly 5/7 fused ketones, while 2-methyl dienones give spiro ketones; unsubstituted dienones give a mixture containing nearly equal amounts of both. In each case, the principal product is the one bearing the methyl group on the newly-formed double bond.

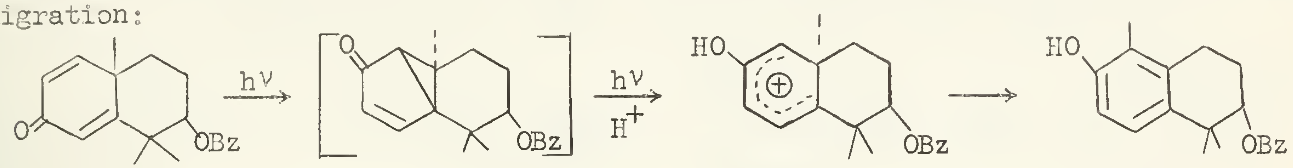
These findings, Kropp maintains, support the contention that the intermediate q serves as a common precursor of both types of ketones and that the methyl group directly affects the mode of cleavage of the cyclopropane ring. He has proposed that the inductive effect of the methyl group may lead to localization of the positive charge of q at the substituted position, or that the methyl group stabilizes the incipient double bond by hyperconjugative effects.[15]

Phenol formation: In many of the transformations described, phenols have been formed as additional products upon the irradiation of cross-conjugated dienones. Many of these compounds can be accounted for by the theories of Chapman and Zimmerman. Kropp has proposed a mechanism to account for variations in phenolic product with substituents on the B ring of dienones.[20] This process, which is somewhat similar to the acid-catalyzed dienone-phenol rearrangement, can be described as follows for the conversion of XX to XXII via the "lumi" product XXI: Irradiation and protonation of the "lumi" product forms the cation r, which rearranges to the spiro intermediate s; as in the regular dienone-phenol rearrangement, migration of the more highly-substituted bond of the spiran, followed by proton loss, gives the phenol. Jeger has proposed a similar process but has noted that many of the phenols are those which would arise by migration



of the least-substituted bond of a spiran intermediate.[14]

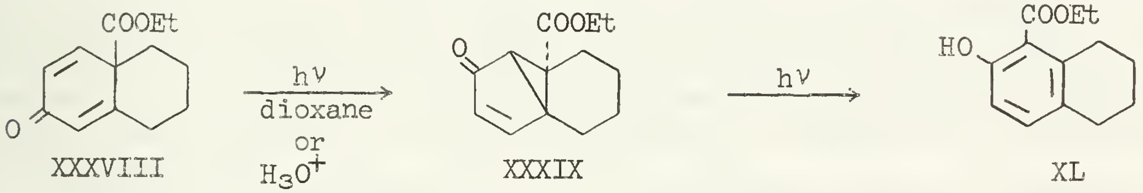
Studies of the dienone-phenol rearrangement have indicated that, when spiran formation is hindered for steric reasons, alternate processes such as alkyl migration occur.[20] Accordingly, the photolysis of XXVII leads to the phenol formed by methyl migration:



XXVII XXX

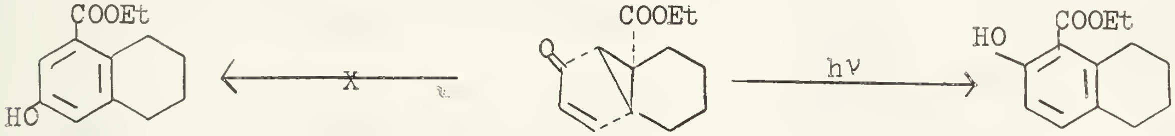
In santonin, Kropp suggests, the trans-fused γ-lactone ring would lead to a highly-strained spiran; thus, methyl migration occurs instead, leading to the observed linearly-conjugated dienone XI.

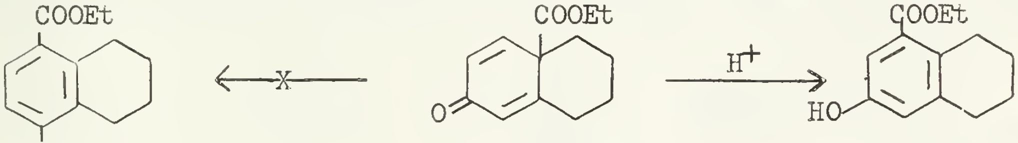
Effects of other substituents: A number of reports have been published of the photoisomerization of dienones bearing substituents other than simple alkyl groups. The irradiation of the dienone XXXVIII, containing a carbethoxy group at C-10, has been reported by Kropp.[23] Unsubstituted dienones tend to give mostly "lumi" product upon irradiation in non-aqueous solvents with a low pressure mercury vapor lamp; in aqueous acidic solvents, similar treatment leads to spiro and 5/7 fused ketones. Similar irradiation of XXXVIII in either dioxane or aqueous acid gives XXXIX as the only ketonic product: only traces of hydroxy ketones could be detected in aqueous acid. Referring to the reaction scheme proposed earlier by Kropp, it appears that the presence of the carbethoxy group favors reaction by path A to the exclusion of the other processes.



XXXVIII XXXIX XL

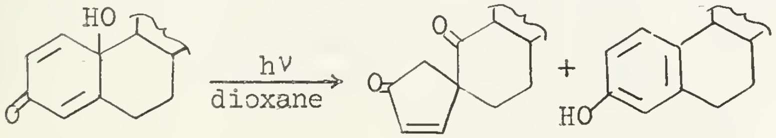
In both solvents, the phenolic product XL was formed; studies showed that this compound could arise directly from the "lumi" product. The formation of XL is surprising in that, formally at least, it involves the 1,2-migration of a carbethoxy group instead of rearrangement through a spiro intermediate. The acid-catalyzed dienone-phenol rearrangement of XXXVIII, however, occurs in a similar manner. Instead of the phenol XLI, expected to form via a spiro intermediate, the principal product is that resulting from formal 1,2-carbethoxy migration (XLII).[24]



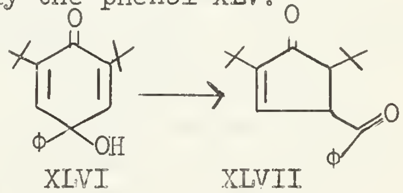


XLI XXXVIII XLII

When irradiated in dioxane with a low-pressure lamp, the 10β-hydroxy dienone XLIII gave the spiro diketone XLIV and the phenol XLV.[25] Under the same conditions, the 10β-acetoxy analogue had been observed to decompose to give only the phenol XLV.[26]



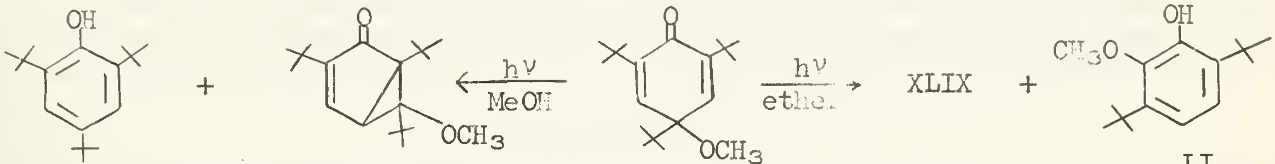
XLIII XLIV XLV



XLVI XLVII

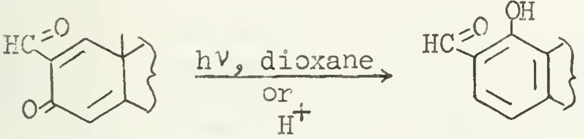
The quinol XLVI gives a product identified as XLVII upon irradiation through Pyrex in aqueous dioxane.[27]

The quinol ether L behaves in a somewhat more complex manner.[28] Upon irradiation in methanol, there can be isolated the "lumi" product XLIX and the phenol XLVIII. In ether, a small amount of "lumi" product is formed, the major product being a phenol resulting from loss of a t-butyl residue; the structure LI has been assigned to this compound. A low-pressure mercury vapor lamp was used for both experiments.

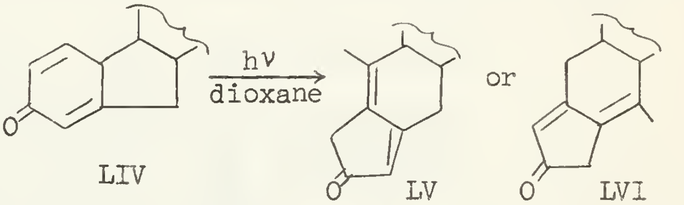


XLVIII XLIX L LI

Jeger has reported that irradiation of LII in dioxane with a high pressure mercury vapor lamp gives the phenol LIII, which can be formed also by acid-catalyzed dienone-phenol rearrangement of LII.[29]



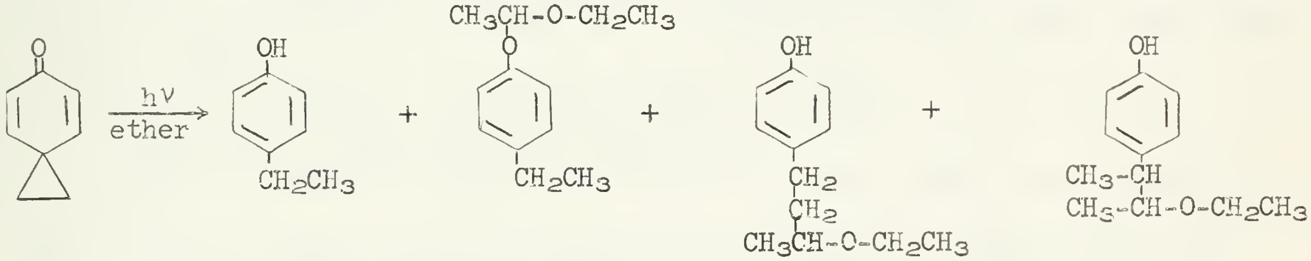
LII LIII



LIV LV LVI

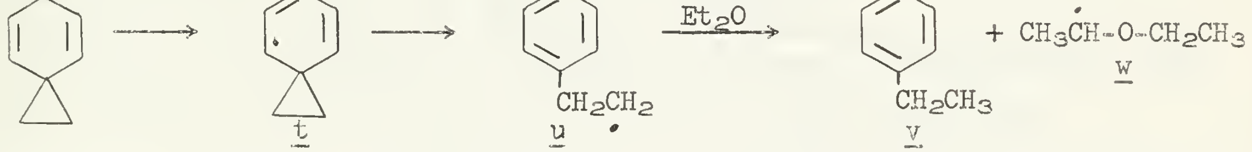
Irradiation of the B-nor dienone LIV in dioxane with a low-pressure mercury vapor lamp leads to a product which, based upon physical and chemical data, could be either LV or LVI.[30] The effect of the size of the B ring is especially evident, since the unsubstituted dienone XVIIc gives mainly "lumi" product under such conditions. This reaction also represents the first non-hydrolytic expansion of the B ring observed in dienone photolyses.

Especially interesting is the report by Schuster that the irradiation of the spiro dienone LVII (through a Pyrex filter) in ether leads to compounds LVIII through LXI:[31]



LVII LVIII LIX LX LXI

The formation of these products may be explained by free-radical intermediates. Irradiation of LVII might lead to a di-radical such as u, either directly or via t; u could then abstract hydrogen from ether to give radicals v and w, which could form the first two products by hydrogen abstraction and coupling. The authors have also suggested



that LX might be formed via an unprecedented carbon-carbon radical displacement by w on LVII, followed by hydrogen abstraction. Formation of LXI may require a 1,2-hydrogen migration; somewhat more likely is hydrogen abstraction from the benzylic carbon of LVIII, followed by coupling of the resulting radical with w. Although the products formed suggest that n → π* excitation of LVII may lead to di-radical intermediates, it is not possible to generalize that such a process occurs with other dienone systems.

Conclusion: Although the studies of dienone photolysis which have been described in this abstract indicate some trends which have been observed in product formation (e.g., the 2- or 4-alkyl effect), they do not resolve the conflicting theories concerning the

nature of the excitation and the excited state, or the processes which the excited states undergo. In fact, some of these results further complicate the problems to be solved; light sources must be taken into consideration, along with solvent and substituent effects. Although n → π^* excitation is a reasonable suggestion for irradiations performed through Pyrex, other processes are likely to be involved in the photoisomerizations resulting from the unfiltered light from a high pressure mercury vapor lamp, or from the nearly monochromatic light from a low pressure mercury vapor lamp. It is hoped that future studies will soon lead to a clarification of these processes.

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The Hammett Acidity Function

Reported by R.P. Quirk December 14, 1964

Introduction - The Hammett acidity function dependency of acid-catalyzed reactions is used as a means of categorizing reactions mechanistically.[1,2] It also serves as a calibration scale for the determination of the base strengths of weak organic bases. Both of these applications necessarily depend upon the applicability and validity of the H_0 acidity scale. This seminar will attempt to critically evaluate the H_0 acidity function and its applications. The use of the acidity function for the determination of base strengths has recently been reviewed by Arnett.[3] Reviews dealing specifically with the acidity function[4,5] and its applications in kinetics[6,7] are also available.

The H_0 acidity scale - The Hammett acidity function, derived from consideration of the protonation equilibria of a class of uncharged basic indicators,

$$B + H^+ \rightleftharpoons BH^+$$

is defined by[5]

$$H_0 \equiv pK_{BH^+} - \log I = -\log a_{H^+} f_B/f_{BH^+} = -\log h_0$$

where pK_{BH^+} refers to the acid dissociation constant, I is the indicator ratio which is the concentration ratio of the indicator in its acidic and basic forms, a_{H^+} is the activity of the hydrogen ion, and the f's refer to the respective activity coefficients. The overlap procedure for determining the pK_{BH^+} of successively weaker bases in concentrated acidic solutions and thus relating them back to the standard state of dilute aqueous solutions is based on the fundamental assumption that the activity coefficient ratio f_B/f_{BH^+} is independent of the structure of the indicator.

Thermodynamic reliability of pK values determined by the overlap method - The overlap procedure of relating all the equilibrium constants and the acidity function to dilute aqueous solution as a standard state implies that log I versus $\boxed{H_0}$ plots for any indicator base would be parallel to that of the most basic indicator all the way to the standard state.[8] However, there is no assurance of parallelsim of indicator ratio plots beyond the range of experimental observation.[3,9] Hogfeldt's work[10] on the possibility of complex formation between molecular H_2SO_4 and water is an example where the equilibrium constants found at high ionic strengths and thermodynamic constants obtained by extrapolation may not refer to the same species. The possibility of specific solvation of the nitro group, which will be discussed later, indicates that the thermodynamic data for all nitrated indicators are probably not referable to an aqueous standard state.

Generality of the H_0 acidity scale- The original H_0 scale was based on a visual colorimetric determination with such diverse species as 1°, 2°, and 3° amines, azo compounds, ketones, and quinones. Because the activity coefficient postulate did not seem to be valid with certain of these species, Jorgenson and Harter[11] have re-evaluated the H_0 acidity scale in H_2SO_4 with a series of primary aniline indicators. The reliability of this new scale is questionable, however, in view of the fact that Boyd[12] has shown that polynitro indicators, such as those used by Jorgenson above 60% H_2SO_4, have significantly different indicator ratio slopes from mononitro indicators as shown in Table I; therefore, polynitro indicators are not reliable Hammett bases.

Table I

Protonation Equilibrium data in H_2SO_4 at $25^\circ \pm 0.02^\circ$

Indicator	2,4-Dichloro-6-nitroaniline		2,4-Dinitroaniline		
conc. H_2SO_4 (Wt.%)	log I	dlog I/d%H_2SO_4	conc. H_2SO_4 (Wt.%)	log I	dlog I/d%H_2SO_4
34.6	-0.983	0.071	51.5	-0.945	0.112
40.7	-0.553	0.079	55.2	0.514	0.120
46.9	-0.066	0.096	58.9	0.071	0.115
52.4	0.462	0.100	62.6	0.355	0.104
57.4	0.965	0.098	65.8	0.688	0.095

A clear indication of how serious an error can be made by assuming applicability of the H_0 scale for molecules of slightly different structure has been presented by Arnett and Mach.[13] They have shown that tertiary aromatic amines do not function as Hammett bases. The divergent behavior of tertiary amines receives support from Boyd's activity coefficient data[12] which are represented in figure 1.

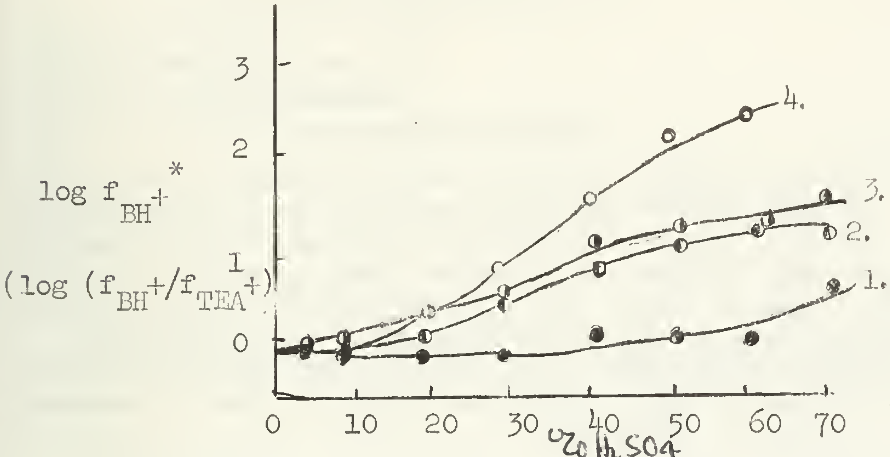


Figure 1. Effect of N-substitution on anilinium ion activity coefficients:

1. N,N,N-trimethylphenylammonium ion
2. N,N-dimethylanilinium ion
3. N-ethylanilinium ion
4. anilinium ion

(TEA^+ is the tetraethyl ammonium ion which was chosen as a standard ion.)

Other examples of classes of compounds which have been found to follow other acidity function behavior include the indoles,[8] the amides,[14] certain substituted azulenes,[15] certain uracils,[16] some aromatic carbonyl compounds,[17] and the pyrroles.[18] Arnett[3] has reviewed other examples which were published prior to August 1, 1962. An indication of the possible magnitudes of errors resulting from the indiscriminate application of the H_0 acidity scale is given in Table II; the absolute values of the acidity function variations, $|H_x - H_0|$, represent approximate orders of magnitude only. Thus, reports which assume the applicability of the H_0 scale, such as the work of Gallo[19] on the basicity of some imidazoles, are of questionable validity.

Table II. Acidity Function Variations

Compounds (X)	Wt. % H_2SO_4	$\lvert H_x - H_0 \rvert$
amides[14]	50	1.0
	82	3.0
indoles[8]	71	2.0
3° amines[13]	50	1.0
	80	2.0

Activity coefficients and the activity coefficient postulate - Deno and Perrizzolo[20] found that $d\log f/ d\%H_2SO_4$ for neutral aromatic compounds did not generally vary more than 0.02 units from 0 to 60% H_2SO_4. A very elegant determination of activity coefficients from solubility data has been carried out by Boyd.[12] It was found that the activity coefficient postulate was valid for indicators consisting of aniline substituted in the ring with one nitro group and halogens. The results obtained for other indicators will be discussed in connection with the effects of solvation upon the acidity function dependency of indicators.

Anomalous behavior of nitro-substituted indicators - Hammett and Chapman[9] observed that nitrated aromatic compounds exhibited sharp increases in solubility in strong aqueous acid. They presented colorimetric and cryoscopic evidence to show that this effect was not due to protonation of the base. Boyd's data[12] also show that the activity coefficient behavior of aniline indicators with two or three nitro groups is quite different from that of the corresponding mononitroanilines. The indicator ratio plots in the region of overlap for these two classes are not parallel, as indicated in Table I., and an inconsistency in the order of 10-20% is thereby introduced into H_0. Arnett and Bushick[21] have noted that very high entropy changes accompany the H_2SO_4-induced ionization of nitrosubstituted triphenylcarbinols relative to the nonnitrated alcohols; representative data from this report are listed in Table III.

Table III.

Entropy of Ionization of Triarylcarbinols at 25°± 0.01°

Alcohol	ΔS^o cal./mole deg.
4, 4', 4''-Trimethoxytriphenylcarbinol	-12.10±1.9
Triphenylcarbinol	+18.02
4-Methyltriphenylcarbinol	+11.08
4-Nitrotriphenylcarbinol	+46.12
4, 4', 4''-Trinitrotriphenylcarbinol	+139.13

These results indicate that there are probably specific solvent interaction effects associated with nitro groups, and that the H_o acidity scale is probably limited to primary mononitroaniline indicators. In addition, the acidity range above 60% sulfuric acid may not be reliable because many acidity functions[11,13,14,21] have relied upon polynitro substitution to study this range of acid concentration.

The effects of added salts on activity coefficients - Paul[22] and Long and McIntyre[23] found that the activity coefficient behavior of Hammett bases in HCl in the presence of added electrolyte followed the Setchenov equation[24]

$$\log f_B/f_B^0 = k_s C_s$$

where f_B/f_B^o represents the ratio of the activity coefficient of the free base in the salt solution to its activity coefficient in pure water, k_s is the salting-out constant, and C_s is the concentration of added electrolyte. Paul also found that the variation of H_o with added electrolyte could be accounted for primarily in terms of the variations in the $\log f_B$ term.

Hydration models - Bascombe and Bell[25] proposed that the difference between pH and the acidity function ("hyperacidity") could be explained in terms of hydration changes. They representedthe equilibrium determining the acidity function as

$$B + H(OH_2)_n^+ \rightleftharpoons BH^+ + nH_2O$$

where n is the number of water molecules liberated on protonation of the base, H_2O represents molecules of water which are not bound to other molecules or ions, and $H(OH_2)_n^+$ is a hydrated proton. On the basis of this model they derived the equation

$$-H_o - \log [H(OH_2)_n^+] + n\log a_w = \log [f_B f_{H(OH_2)_n^+}/f_{BH^+}]$$

where a_w is the activity of water, and $f_{H(OH_2)_n^+}$ is the activity coefficient of the hydrated proton. Bascombe and Bell identified the concentration of the proton hydrate $[H(OH_2)_n^+]$ with $[H^+]$, the molar hydrogen ion concentration. When the quantity on the left side of the above equation with $n = 4$ was plotted versus $[H^+]$ up to 8 molar, a straight with a slope of about 0.1 was obtained. This is consistent with the variation expected for the activity coefficient term, i.e., adherence to the Setchenov equation.

Perrin[26] has extended the hydration treatment of Bascombe and Bell by allowing for a variable overall hydration change upon protonation of a neutral base with changing acid concentration. The standard state for every proton hydrate was chosen so that in dilute solution $a_{H(OH_2)_n^+}$ approaches $[H^+]$, the stoichiometric hydrogen ion concentration. Thus,

$$a_{H^+} a_w^n = a_{H(OH_2)_n^+}$$

and

$$h_o = a_{H^+} f_B/f_{BH^+} = \frac{[H(OH_2)_n^+] f_{H(OH_2)_n^+} f_B}{a_w^n f_{BH^+}}$$

where $[H(OH_2)_n^+]$ is the concentration of the proton-n hydrate, and $a_{H(OH_2)_n^+}$ is the activity of the proton-n hydrate. When n can assume several values, the more general relationship

$$[H^+] = \sum_n [H(OH_2)_n^+]$$

must be used. Perrin's model further assumed that the ratio, $[H^+]/h_o$, could be expanded in a power series in water activity; thus,

$$[H^+]/h_o = \sum_n q_n a_w^n$$

where the quantity

$$q_n = f_{BH^+}/ f_{H(OH_2)_n^+} f_B$$

was assumed to be medium independent. Using this model Perrin was able to show that

$$\frac{d(-H_o - \log[H^+])}{d(-\log a_w)} = \frac{\sum_n n[H(OH_2)_n^+]}{\sum_n [H(OH_2)_n^+]} = \bar{n}$$

Thus, this model identifies the slope of the hyperacidity versus -log a_w plot with the average hydration change accompanying protonation. This plot is shown in figure 2.

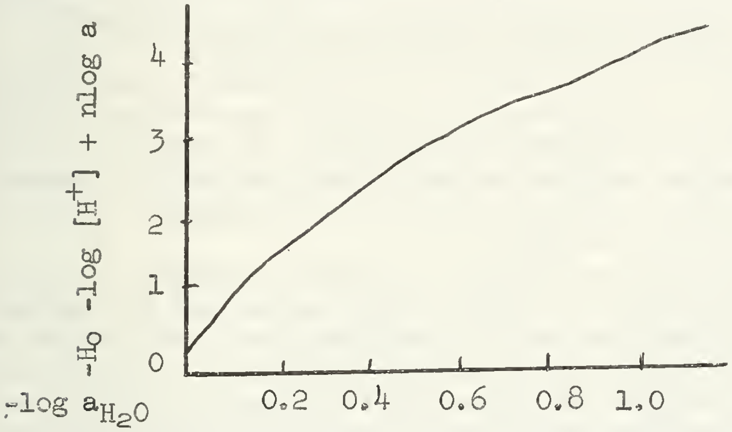


Figure 2.

The effects of added salts on the acidity function-Rosenthal and Dwyer[27] applied a Bascombe and Bell treatment of hydration to explain the acidity function in dilute solutions of HCl with added LiCl up to 9 M and obtained the expression,

$$H_o = -\log [H^+] + n \log a_w - B C_s$$

where B is a salting-out constant, C_s is the concentration of added salt, and $[H^+]$ represents the molar concentration of acid.

Wyatt and Ojeda[28] have explained the variation of H_o in HCl solutions in the presence of high salt concentrations by extending a hydration treatment previously developed by Wyatt[29] for concentrated acid solutions. The equilibrium which they considered was

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O$$

It was assumed that the activity coefficient ratio $f_{H_3O^+}/f_{BH^+}$, where $f_{H_3O^+}$ is the activity coefficient of proton monohydrate, was independent of medium. The resulting expression for H_o in terms of this model is

$$H_o = -\log f_B - k - \log X_{H_3O^+} / a_w$$

where the concentration of proton monohydrate is in mole fraction units to offset the units for water activity in the above equilibrium, and -k is the difference between pK_{BH^+} and the pK of the equilibrium defined above for this model. The proton monohydrate was regarded as being able to take on four molecules of water in stages whose respective equilibrium constants were determined only by statistical factors. The total acid concentration must then be equal to the sum of the concentrations of all the hydrated species

$$C_{H^+} = C_{H_3O^+} (1 + 20a_w + 150a_w^2 + 500a_w^3 + 625a_w^4)$$

where C_{H^+} is the total acid concentration, $C_{H_3O^+}$ is the concentration of the proton monohydrate, and the numbers represent products of the equilibrium constants. Using the assumption that the activity of water was equal to the mole fraction of free water molecules in solution, Wyatt obtained the expression,

$$H_o + \log f_B + k = -\log \left[\frac{C_{H^+}(1-a_w)}{a_w(vC + 2C_H^+)(1 + 20a_w + 150a_w^2 + 500a_w^3 + 625a_w^4)} \right]$$

where v is equal to the number of ions per molecule of salt, and C is the concentration of added salt. This equation was compared with the data obtained for the various salt solutions. The log f_B terms were evaluated by means of the Setchenov equation. The

calculated and experimental values of the quantity $H_o + \log f_B$ were within ± 0.1. Contrary to the results of Paul[22] mentioned previously, Wyatt thus found that eliminating the salting-out effect on H_o left a larger effect, which was interpreted in terms of dehydration of the hydrogen ion as the water activity was reduced.

Support for these models which assume that the overall hydration changes accompanying protonations are a variable has been presented by Dunford.[30] Dunford has been able to account for the acidity of H_2SO_4- H_2O solutions in terms of proton hydrates containing from one to six waters of hydration. It was found that the average hydration number goes through a maximum at approximately 3M H_2SO_4 and then decreases. The main criticism of these hydration treatments is that the average hydration number may be sensitive to the choice of indicator and thus the activity coefficient ratio may vary with indicator structure.

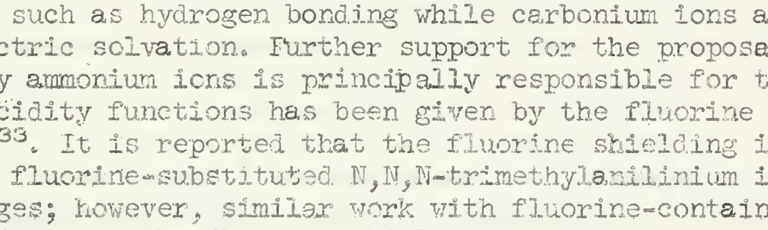
Comparison of the H_o and H_R acidity scales - Solvation changes are most clearly indicated by enthalpy and entropy factors. Therefore, it is worthwhile to compare these thermodynamic functions for the H_o and H_R[31] acidity scales in order to understand the difference between solvation of ammonium ions and carbonium ions. Arnett and Bushick[21] have determined the equilibrium constants for a series of triarylcarbinol-carbonium ion systems in H_2SO_4-H_2O solutions at various temperatures. It was found that the behavior of these compounds was in rough agreement with a simple electrostatic treatment,[1] i.e.,

$$\Delta S^o = \Delta F^o \ (d\ln D/dt)$$

where the quantity (dlnD/dt) represents the derivative of the log of the dielectric constant of the medium with respect to temperature; this quantity is equal to -4.63×10^{-3}, for water. The slope obtained for the arylcarbinols was -4.6×10^{-3}, which is to be compared with a value of -1.5×10^{-3} obtained for the primary aniline indicators studied by Gelbstein[32] This indicates that the interaction af anilium ions with the solvent is through more specific interactions such as hydrogen bonding while carbonium ions are probably solvated through general dielectric solvation. Further support for the proposal that the hydrogen bonding interaction by ammonium ions is principally responsible for the difference between the H_R and H_o acidity functions has been given by the fluorine magnetic resonance work reported by Taft[33]. It is reported that the fluorine shielding in the p-fluorobenzyl carbonium ion and the fluorine-substituted N,N,N-trimethylanilinium ions is not affected by medium changes; however, similar work with fluorine-containing BH^+ cations has shown large medium effects on the fluorine shielding.

Other evidence indicating specific solvent interactions with ammonium ions - Boyd's activity coefficient data[12] indicate that anilinium ions are appreciably solvated and that their solvation differs with the degree of substitution of the nitrogen atom of the aniline base; the data were represented in figure 1. Arnett[13] found that the acidity function for tertiary amines was between the H_o and H_R acidity functions; thus, removal of acidic hydrogen atoms results in solvation behavior which approaches that of carbonium ions. In addition, Schubert[34] has found that successive replacement of methyl groups by hydrogen in the trimethylethers of phloroglucinol shifts the acidity function dependency toward that of a Hammett base.

Taft[35] obtained linear relationships by plotting $H_R - H_o$ versus $-\log a_w$. The results were explained in terms of the different degrees of specific solvation of the primary and secondary anilinium ions versus carbonium ions, and were indicative of the following equilibria:



$$[Ar{-}N(H\cdots OH_2)_3]^+ + ROH \rightleftarrows ArNH_2 + R^+ + 4\ H_2O$$

$$[Ar_2N(H\cdots OH_2)_2]^+ + ROH \rightleftarrows Ar_2NH + R^+ + 3\ H_2O$$

The individual equilibria being considered are

$$H_2O + R^+ \rightleftarrows \text{alcohol} + H^+$$

$$BH(OH_2)_n^+ \rightleftarrows H^+ + n\ H_2O$$

and the corresponding acidity functions are

$$H_R = -\log a_{H^+} - \log f_{ROH} + \log f_{R^+} + \log a_w$$

$$H_0 = -\log a_{H^+} - \log f_B + \log f_{BH(OH_2)_n^+} - n\log a_w$$

from which the difference between the acidity functions can be evaluated as

$$H_R - H_0 \simeq \log f_B/f_{ROH} + \log f_{R^+}/f_{BH(OH_2)_n^+} + (n+1)\log a_w$$

If the activity coefficient terms are neglected, the difference between the acidity functions for the amines of different degrees of substitution can be related to the apparent average differences in degrees of hydration. However, Arnett[13] has recently shown that the linear plots and integral hydration differences obtained by Taft were a result of the narrow acid concentration range used, and that these hydration factors are a function of the medium as shown in Table 4, where $n^{1°}$ is the apparent hydration number of a primary amine indicator and $n^{3°}$ is the apparent hydration number of a tertiary amine indicator.

Table 4. Hydration factors

% H_2SO_4	$n^{1°}$ *	$n^{3°}$ **
10	13.4	6.8
20	12.8	5.4
30	8.2	4.4
40	4.1	2.7
50	2.6	2.7
60	1.9	0.9
70	0.6	0.2

The H_0 acidity function in aprotic solvents - Arnett and Douty[36] have obtained an acidity function scale with H_2SO_4 in sulfolane (tetramethylenesulfone), although the activity coefficient postulate was not rigorously upheld. The results obtained parallel the behavior of the acidity function in nitromethane reported by Hammett.[37] These results are surprising in view of the fact that there is evidence that sulfuric acid is functioning not only as a proton donor, but also as a hydrogen-bond donor. The applicability of the activity coefficient postulate is in doubt, however, because it has not been shown that the acidity function is independent of the structure of the acid.[38,39]

The Bunnett application of acidity function dependence of reaction rates - Bunnett[40] has determined the slopes of the plots of [log (rate constant + H_0)] versus log a_w for many reactions and has proposed that the empirical correlations obtained be applied as mechanistic criteria. Bunnett has designated these slopes as "ω" values, and interpreted them in terms of the hydration of the transition state less the substrate (unprotonated base) on a scale set by the "water balance in protonation of an indicator base. The reaction sequence considered is:

$$S(OH_2)_s + H(OH_2)_n^+ \rightleftharpoons SH(OH_2)_p^+ + (s+n-p)H_2O \quad \text{Equilibrium}$$

$$SH(OH_2)_p^+ + (t-p)H_2O \rightleftharpoons \ddagger(H_2O)_t^+ \quad \text{rate determining}$$

$$\ddagger(H_2O)_t^+ \longrightarrow \text{products} \quad \text{Fast}$$

The resulting rate law is

$$\text{rate} \simeq k_\psi[S]_{total} \simeq \frac{k}{K_{SH^+}}[S(OH_2)_s][H(OH_2)_n^+]a_w^{(t-s-n)} \frac{f_{S(OH_2)_s} f_{H(OH_2)_n^+}}{f_{\ddagger(H_2O)_t^+}}$$

When very little of the substrate is protonated, the following relationship applies

$$k_\psi \simeq \frac{k}{K_{SH^+}} [H(H_2O)_n^+]a_w^{(t-s-n)} \frac{f_{S(OH_2)_s} f_{H(OH_2)_n^+}}{f_{\ddagger(H_2O)_t^+}}$$

The acidity function obtained from a Bascombe and Bell hydration treatment is

$$h_0 = \frac{[H(H_2O)_n^+] f_{B(H_2O)_b} f_{H(H_2O)_n^+}}{a_w^{(b+n-a)} f_{BH(H_2O)_a^+}}$$

where the lower case letters refer to the hydration numbers of the respective species. By substituting the value of $[H(OH_2)_n^+]$ from the acidity function, the rate constant expression becomes

$$k_\psi = \frac{k}{K_{SH^+}} h_o a_w^{(t-s+b-a)} \quad \frac{f_{S(H_2O)_s} f_{BH(H_2O)_a^+}}{f_{B(H_2O)_b} f_{\ddagger(H_2O)_t^+}}$$

It can now be seen that $\omega \simeq (t-s) - (a-b)$

The validity of interpreting the ω values in terms of the mode of involvement of water in the rate determining step depends upon the constancy of the above hydration difference, $(t-s) - (a-b)$. Hydration treatments have shown that the quantity $(a-b)$ is strongly dependent upon the medium, and this would apply also to $(t-s)$; thus, ω would not be expected to be independent of medium except in the most favorable cases. Evidence has also been presented which has shown the limited generality of the acidity scale. The difference in activity coefficient behavior of various substrates seems to be very dependent upon their modes of solvation. Thus, it is to be expected that variations in ω would arise from different activity coefficient behavior of the reactant from that of a Hammett base.

Conclusion - The present H_o acidity function can be used with rigor only for primary aniline indicators containing one nitro group and halogen substitution in view of the specific influences of the nature of the basic group and other substituents on the activity coefficient behavior of the free and protonated base. The limitations which have been found for the acidity function apply also to its use in kinetics. In addition, the interpretation of Bunnett's ω values is questionable. Probably the most encouraging prospect for the acidity function will be its use in understanding the effects of substrate structure on solvation. The understanding of the effects of acid concentration on kinetics awaits the study of model systems for the substrates and the transition states in terms of activity coefficient behavior.

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The Mechanism of the Kolbe Reaction

Reported by Jeremy A. Klainer January 7, 1965

Introduction: The classical Kolbe reaction can be represented by the following scheme:

$$2C_nH_{2n+1}CO_2^{\ominus} \xrightarrow{2e^{\ominus}} 2CO_2 + C_{2n}H_{4n+2} + \text{side products} \qquad \text{I}$$

The hydrocarbon, $C_{2n}H_{4n+2}$, referred to as the Kolbe product, is accompanied by side products which include alcohols, alkanes, esters, olefins, and rearranged products. Many reviews have appeared concerning the synthetic aspects of the reaction, its limitations, scope and utility.[1-6] This seminar will give a brief description of historical proposals and will concentrate on recent work concerned with the nature of the electrode process and the production of carbonium ions by Kolbe electrolysis.

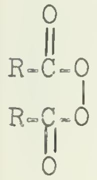
Historical Background: The nature of the Kolbe product as well as product studies in the presence of trapping agents indicate a radical mechanism. Smith and Gilde isolated over twenty compounds in the electrolysis of potassium acetate in the presence of butadiene. All products could be rationalized by a radical mechanism. Three of the plausible mechanisms, the acyl peroxide, the hydrogen peroxide and the discharged ion theories have received some experimental validation. They hydrogen peroxide theory for aqueous solutions can be illustrated by the following scheme:

$$2OH^{\ominus} \longrightarrow H_2O_2 + 2e^{\ominus} \qquad \text{II}$$

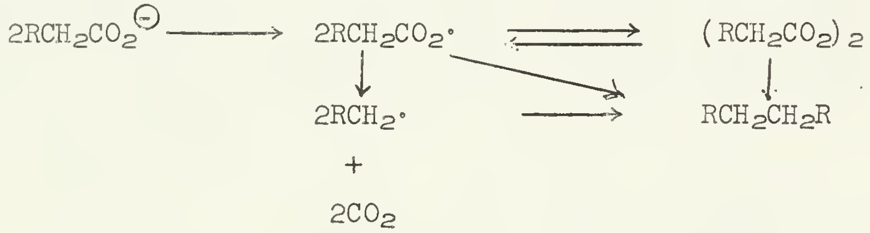
$$2CH_3CO_2^{\ominus} + H_2O_2 \longrightarrow 2OH^{\ominus} + 2CH_3CO_2\cdot \qquad \text{III}$$

$$2CH_3CO_2\cdot \longrightarrow 2CO_2 + C_2H_6 \qquad \text{IV}$$

This theory was discredited by showing that hydrogen peroxide gave oxygen instead of the Kolbe product when added to the electrolyte under reaction conditions.[7,8] The acyl peroxide theory proposed an acyl peroxide of form (1) as an intermediate. The evidence for this was the isolation of dihexanoyl peroxide by Fitcher in the electrolysis of potassium hexanoate at -20° C.[9] Khomutov and Khachaturyan reported the formation of acetyl peroxide on the surface of the electrode in the electrolysis of 5M potassium acetate at -40° C.[10] All the data above can be explained by a direct discharge mechanism with reversible formation of the acyl peroxide as illustrated in the following scheme for $RCH_2CO_2^{\ominus}$.



(1)



V

Kinetic and Electrode Phenomena Studies: Although the Kolbe reaction is thought to go through a radical mechanism, very little is known about the actual processes on the electrode surface. In the following studies, all the workers tried to elucidate these phenomena. Wilson and Lippincott tried to study the molecularity of the rate determining step in the electrolysis of aqueous and nonaqueous acetic acid-acetate systems and in aqueous propionic acid-propionate system using alternating current. The use of alternating current gave a method of distinguishing between first and second order rate determining steps. Figure 1 shows three frequencies of f, 2f, and 4f. Since radicals are produced only along the top bar the number of radicals produced in each of these cycles will be in the ratio of 4:2:1. However, by allowing the cycles to be repeated n, 2n, 4n respectively the total number of radicals produced will be the same in each case. The radicals cannot last from one cycle to another and are either destroyed by reacting or by being reduced when the current changes. Therefore, the frequency dependence of a second order reaction will be greater than that of a first order reaction because the radicals must

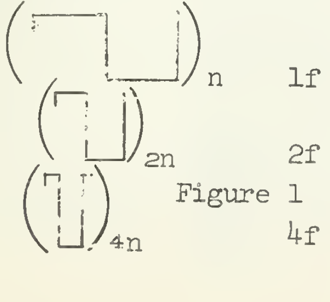


Figure 1

pair up in order to react.

For the following reactions: $R\cdot \xrightarrow{k_1}$ product; $2R\cdot \xrightarrow{k_2}$ product VIa,b the authors derived the following expressions for current efficiency, where current efficiency is defined as:

$$\frac{\text{concentration of product/cycle}}{\text{current/cycle}}$$

For first order (eq. VIa) current efficiency $= 1-(f/k_1)(1-e^{-k/t})$ VIIa

For second order (eq. VIb) current efficiency $= 1/4f(f-\sqrt{Ik_2})-f \log 2/Ik_2$ VIIb

Where f is the frequecny, k_1 and k_2 are the respective rate constants for the first and second order reactions, and I is the equivalents of electricity/sec. cm^2. The results are shown in Table I.

Table I

Current efficiences for Carbon Dioxide and Hydrocarbon Product Indicated.

Solution #	I		II		III		IV		Solution Composition
Frequecny c.p.s.	C_2H_6	CO_2	C_2H_4	CO_2	C_2H_6	CO_2	C_2H_6	CO_2	
2	86.6	91.3	68.3	84.3					I = 0.5 M KOAc, 5.0M HOAc in water; current density 0.45 amp/cm^2. II = 0.5M KO_2CEt, 5.0M HO_2CEt in water; current density 0.45 amp/cm^2. III = 1.0 KOAc in HOAc current density 0.8 amp/cm^2. IV = 0.5M KOAc, 7.5M HOAc in water; current density 0.8 amp/cm^2.
7	85.4	90.8	48.2	63.2	92.5	91.2			
15	85.0	90.0	40.0	55.4	92.0	90.4	88.4	92.6	
25	84.3	89.4	36.3	51.6					
30	83.6	88.7	34.4	49.5	93.2	91.0	88.6	93.5	
40	82.1	87.2	33.2	47.8			87.3	92.5	
50	81.6	87.0	32.4	47.0	92.6	92.4	88.2	91.9	
69	80.7	86.5	30.8	46.5	93.8	91.8			
80	79.2	84.8	30.2	46.5					

Wilson and Lippincott then compared the empirical efficiency of hydrocarbon formation with those expected from equations(VIIa,b). Their treatment was not rigorous and no attempt was made to evaluate the rate constants. Conclusions that can be drawn are that the dependence of current efficiency upon frequency is the same in aqueous and non-aqueous solutions (i.e. III and IV) and that the molecularity for ethylene production is different than that for ethane.

The authors reported that the only product obtained in the electrolysis of propionic acid at 25°C in water was ethylene. The low product efficiency indicates that either water is being discharged or soluble products are being formed. In light of the absence of ethane the authors proposed the following biradical mechanism for the formation of ethylene:

$$C_2H_5COO\cdot + CH_3CH_2CO_2\cdot \longrightarrow CH_3CH_2CO_2H + \cdot CH_2\text{-}CH_2CO_2\cdot \longrightarrow CO_2 + CH_2{=}CH_2 \quad \text{VIII}$$

The biradical could be stabilized on the electrode surface but these observations can be explained in other ways, one being oxidation to the carbonium ion and attack by the anion of the acid ($B^{\ominus}$) as follows:

$$C_2H_5CO_2^{\ominus} \longrightarrow C_2H_5CO_2\cdot \longrightarrow \underset{\substack{+\\CO_2}}{C_2H_5^{\oplus}} \xrightarrow{B^{\ominus}} BH + CH_2{=}CH_2 \quad \text{IX}$$

This system may not conform to the molecularity implied by Lippincott's and Wilson's experiment but Pinkerton has pointed out some erroneous assumptions made by Lippincott.[12] Lippincott assumed radicals would be destroyed only by reduction when the current changed and did not allow for the possibility of the radicals reacting after the current reversal. The difference in radical concentration as a function of frequency is shown in Fig. 2. The solid line indicates the radical concentration employing Lippincott's assumption; the dotted line, those of Pinkerton. Pinkerton derived the following expression for current efficiency that is independent of molecularity and is only a function of the frequency f, and the radical destruction relaxation

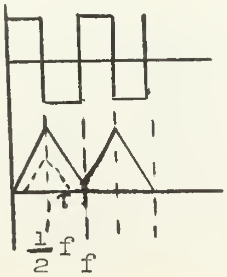


Figure 2.

time τ.

$$\text{Efficiency } (f) = 1-2f(\tau-\tfrac{1}{2}f) \qquad \mathrm{X}$$

Both derivations neglect complicating factors such as diffusion, adsorption and double layer capacitance. If one assumes that the values of τ are approximately equal for aqueous and nonaqueous solutions, the molecularity of systems III and IV would seem to be the same.

Recently a great deal of work has been directed towards the elucidation of the rate limiting step of the reaction and the function of the electrode. The reactions that will be considered are of the general form:

$$\mathrm{Ox.} + ne^{\ominus} \underset{k_a}{\overset{k_c}{\rightleftarrows}} \mathrm{Red.} \qquad \mathrm{XI}$$

Empirically the current for any reaction is the velocity of the reaction times the area of the electrode (A) times the charge involved in reducing one mole of the compound under study. By definition the cathodic current is positive and the anodic current is negative so the total current can be written as: $i = i_c - i_a$ XII
which must be equal to: $i = nFA(k_c C^o_{ox} - k_a C^o_{red})$ XIII
where A is the area of the electrode, F is the faraday, n is the number of electrons involved in the reaction, k_c and k_a are the heterogeneous rate constants experessed as sec cm^{-1}. and C^o_{ox} and C^o_{red} are the surface concentrations of the Ox and the Red species respectively. The specific rate constants at any potential (E) are:

$$k_c = k^o \exp[-\frac{\alpha nF}{RT}(E-E^{o\prime})] \qquad k_a = k^o \exp[\frac{(1-\alpha)nF}{RT}(E-E^{o\prime})] \qquad \mathrm{XIV, XV}$$

where k^o is the value of the rate constant when $E=0$, R is the gas constant, T is the absolute temperature, E is the applied potential and $E^{o\prime}$ is the standard potential. α is a symmetry coefficient that has the range $1>\alpha>0$ and tells what portion of the voltage difference $(E-E^{o\prime})$ favors the cathodic reaction. The over-potential is defined as:

$$\eta = E - Eeq \qquad \mathrm{XVI}$$

where Eeq is given by the Nernst equation.

$$Eeq = E^{o\prime} + \frac{RT}{nF} \ln \frac{C_{ox}}{C_{red}} \qquad \mathrm{XVII}$$

By substitution of equations XIV and XV into XIII, it is derived that:

$$i = nFAk^o \left[C^o_{ox} \exp\left\{\frac{-\alpha nF}{RT}(E-E^{o\prime})\right\} - C^o_{red}\left\{\frac{(1-\alpha)nF}{RT}(E-E^{o\prime})\right\}\right] \qquad \mathrm{XVIII}$$

Combination of equations XVI and XVII and substitution into XVIII gives,

$$i = i_o\left[\frac{C^o_{ox}}{C_{ox}} \exp\left\{\frac{-\alpha nF}{RT}\eta\right\} - \frac{C^o_{red}}{C^o_{red}}\left\{\exp \frac{(1-\alpha)nF}{RT}\eta\right\}\right] \qquad \mathrm{XIX}$$

where i_o is the exchange current at equilibrium.

If the over potential is large, i.e. $\eta > 0$ and if it is assumed that $C^o_{ox} = C_{ox}$ and $C^o_{red} = C_{red}$ then the first term will be very small and the reaction is irreversible. The following equation is derived:

$$i = i_o \exp \frac{(1-\alpha)nF}{RT}\eta \qquad \mathrm{XX}$$

by taking logs and rearranging,

$$\eta_a = \frac{-2.3RT}{(1-\alpha)nF} \log I_o \; \frac{+2.3\,RT}{(1-\alpha)nF} \log ia \qquad \mathrm{XXI}$$

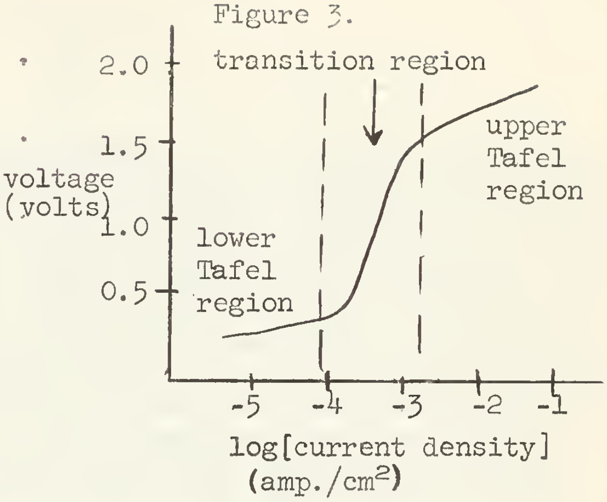
or

$$\eta_a = a + b \log Ia \qquad \mathrm{XXII}$$

This is a Tafel equation and will give a linear plot between potential and the log of the current or log of the current density (Ia). Figure 3 shows a voltage versus log(current density) plot, where the linear portions of the curve can be approximated by the Tafel equation. The linear portion of the curve lying to the lower left will be designated the lower Tagel region; the linear portion to the upper right will be designated the upper Tafel region. The intermediate non linear portion

will be refered to as the transition region.

Figure 3.



By the use of Tafel slopes Conway and Dzieciuch tried to determine the rate determining step in the following reaction:[13]

$$HCOO^{\ominus} \longrightarrow CO_2 + H^{\oplus} + 2e^{\ominus} \qquad XXIII$$

The authors proposed the following mechanisms:

$$\left.\begin{array}{lll} XXIV & M + HCOO^{\ominus} \longrightarrow HCOO\cdot M + e^{\ominus} \\ XXV & HCOO\cdot M \longrightarrow H\cdot M + CO_2 \\ & H\cdot M \longrightarrow H^{\oplus} + e^{\ominus} \\ & HCO_2^{\ominus} + H^{\oplus} \rightleftarrows HCO_2H \end{array}\right\} \text{Scheme A}$$

$$\left.\begin{array}{ll} XXIV & M + HCOO^{\ominus} \longrightarrow HCOOM + e^{\ominus} \\ XXVI & HCOO\cdot M \longrightarrow CO_2 + H^{\oplus} + e^{\ominus} \end{array}\right\} \text{Scheme B}$$

$$XXVII \quad HCOO^{\ominus}M \longrightarrow M + CO_2 + H^{\oplus} + 2e^{\ominus} \Big\} \text{Scheme C}$$

M indicates the electrode surface. The authors ignored other possibilities, including the formation of peroxides.

The authors then derived the theoretical Tafel slopes for each scheme allowing each reaction in turn to be the limiting reaction. The method is illustrated for Scheme A with reaction XXIV rate limiting.[17]

Rewriting equations XIV and XV and substituting β for $(1-\alpha)$ and $\Delta\phi$ for $(E-E^{o\prime})$, for any reaction (i) of the form, $Red \underset{k_{-i}}{\overset{k_i}{\rightleftarrows}} Ox + ne^{\ominus}$, the rates may be expressed as $k_i = k^o e^{\beta\Delta\phi nF/RT}$; $k_{-i} = k^o e^{-(1-\beta)\frac{\Delta\phi nF}{RT}}$. To obtain an expression for the forward rate of the overall electrode reaction, one writes: $v = W_1 - W_{-1}C_{x1}$ XXVIII where $W_1 = k_1C_1$ and C_1 is the concentration of the radical X_1 produced in the first stage of the reaction. Similarly, $v = W_2C_{x1} - W_{-2}C_{x2}$ XXIX where x_2 is the entity produces by the forward direction of the second step. The overall velocity for a series of consecutive reactions is given in the following equation:

$$\frac{1}{v} = \frac{1}{W_1} + \frac{W_{-1}}{W_1W_2} + \frac{W_{-1}W_{-2}}{W_1W_2W_3} + \ldots\ldots\ldots \frac{+W_{-1}W_{-2}\ldots W_{-(n-1)}}{W_1W_2\ldots\ldots\ldots W_n} \qquad XXX$$

Applying the above equations to scheme A the following expressions can be written for the velocities v and the velocity factors W.

reaction velocities	reaction velocity factors
$v_1 = k_1C_{R^{\ominus}}C_M e^{\beta\Delta\phi F/RT}$	$W_1 = k_1C_{R^{\ominus}} e^{\beta\Delta\phi F/RT}$
$v_{-1} = k_{-1}C_{MR} e^{-(1-\beta)\Delta\phi F/RT}$	$W_{-1} = k_{-1}e^{-(1-\beta)\Delta\phi F/RT}$
$v_2 = k_2C_{MR}$	$W_2 = k_2$
$v_{-2} = k_{-2}C_{CO_2}C_{H\cdot M}$	$W_{-2} = k_{-2}$
$v_3 = k_3C_{HM}e^{\beta\Delta\phi F/RT}$	$W_3 = k_3e^{\beta\Delta\phi F/RT}$
$v_{-3} = k_{-3}C_{H^{\oplus}}e^{-(1-\beta)\Delta\phi F/RT}$	$W_{-3} = k_{-3}e^{-(1-\beta)\Delta\phi F/RT}$

By substitution into equation XXX the overall velocity is:

$$v = \frac{k_1k_2k_3C_{R^{\ominus}}e^{2\beta\Delta\phi F/RT}}{k_1k_3e^{\beta\Delta\phi F/RT} + k_3k_{-1} + k_{-1}k_{-2}e^{-(1-\beta)\Delta\phi F/RT}}$$

By letting $k_{-1} \to 0$ and k_1 be rate determining, the following expression is derived:

$$v = k_1C_{R^-}e^{\beta\Delta\phi F/RT}$$

The current is just the charge times the velocity: $i = k_1FC_R\text{-}e^{\beta\Delta\phi F/RT}$ The Tafel slope is then $\frac{\partial\Delta\phi}{\partial \ln i}$ or for the above expression:

$$\frac{\partial\Delta\phi}{\partial \ln i} = \frac{RT}{\beta F}$$

The authors do not mention their method of approximating β yet from their results they must have chosen $\beta = 1/2$. So the theoretical Tafel slope in this case is 2RT/F. The mathematical treatment presented above is only valid under limiting low or limiting high surface coverage. It also does not consider changes in the heat of adsorption of the radical upon the activation energy. The empirical value of 2RT/F for the upper Tafel region was expected in two cases, scheme A with reaction XXIV rate determining and Scheme B with reaction XXVI rate determining and XXIV in equilibrium.

Galvanostatic charging results indicated there was a complete monolayer on the surface. This implies the Scheme A is operative and that the film on the surface is adsorbed HCOO· radicals. Further evidence is the correlation between decay of double layer capacitance and delayed gas evolution of carbon dioxide under open circuit conditions. The loss of capacitance correlated with that theoretically calculated for a HCOO· radical monolayer.[14]

In order to provide a better model, Conway and Dzieciuch studied the trifluoroacetic acid-trifluoroacetate system under aqueous and nonaqueous conditions with platinum electrodes. The observed Tafel slopes were in the range $^{4RT}/_F$ to $^{6RT}/_F$ and depended on the current density and the electrode material used. The following mechanisms were envisaged:

$$2CF_3CO_2^{\ominus} \longrightarrow 2CF_3CO_2\cdot M + e^{\ominus} \qquad \text{XXXI}$$

$$2CF_3CO_2\cdot M \longrightarrow CF_3\cdot M + CO_2 \qquad \text{XXXII}$$

$$2CF_3\cdot M \longrightarrow C_2F_6 \qquad \text{XXXIII}$$

The following desorption steps were also considered:

$$CF_3\cdot + CF_3CO_2^{\ominus} \longrightarrow C_2F_6 + CO_2 + e^{\ominus} \qquad \text{XXXIV}$$

$$CF_3CO_2\cdot + CF_3CO_2^{\ominus} \longrightarrow C_2F_6 + 2CO_2 + e^{\ominus} \qquad \text{XXXV}$$

The authors eliminated the possibility of free acyl peroxide, ester and carbonium ions due to the high coulombic yield of hexafluoroethane (96%). This is invalid since the acyl peroxide could be an intermediate and still give a high yield of hexafluoroethane. Theoretical analysis yielded limiting slopes for the Tafel equation under different conditions as shown in Table II. Column one presents the Tafel slope for the upper portion of the Tafel curve under low or high coverage conditions. These Tafel slopes were derived using the method illustrated on page 157. Intermediate coverage "Temkin conditions" refers to theoretical slope for the upper portion of the Tafel curve where changes in the heats of adsorption of the radical and anion with amount of coverage are considered. "Temkin conditions" refer to the assumption that the non-exponential term of equation XIX will be negligible and can be neglected with respect to the exponential term.

TABLE II

Tafel slopes for rate limiting reactions as a function of surface conditions.

Reaction	Low or high coverage, "Langmuir" conditions	Intermediate coverage "Temkin" conditions
XXXI	2RT/F	2RT/F
XXXII	RT/F or limiting current as coverage $\theta CF_3CO_2\cdot \longrightarrow 1$	$\frac{r_1}{r_1-r_2}$ 2RT/F
XXXIII	RT/2F or limiting current as $\theta CF_3 \rightarrow 1$	$\frac{r_1RT}{2r_2F}$ or $\frac{r_1RT}{f_2F}$ for activated adsorption of C_2F_6 as $CF_3\cdot$
XXXIV	2RT/F for full coverage by $CF_3CO_2\cdot$	2RT/F $\frac{r_1}{r_1+2r_2}$ or 2RT/F $\frac{r_1}{r_1+r_2}$ for activated adsorption
XXXV	2RT/F ($\theta CF_3CO_2\cdot \rightarrow 1$) or 2RT/3F for low coverage	2RT/3F or RT/F for activated adsorption

In Table II, θ refers to the fractional electrode coverage, r_1 refers to changes in the adsorption energy for $CF_3CO_2\cdot$ with coverage where the adsorption energy is given as

$$\Delta H = \Delta H^{o} - r_1\theta \qquad \text{XXXVI}$$

where ΔH° is heat of adsorption with no coverage. The symbol r_2 refers to corresponding changes in the heat of adsorption for $CF_3\cdot$. The authors assumed that surface coverage was high in analogy with the formate case. Galvanostatic charging curves suggested the formation of a fractional monolayer that approaches full coverage as the current increases. This film was assumed to be $CF_3CO_2\cdot$ radicals and on this assumption the authors suggested that reaction XXXI was not rate determining. The observed slope of 4 to 6 RT/F cannot be derived under Langmuir conditions. It is possible to explain the results under Temkin conditions of intermediate coverage by choosing values of r_1 and r_2 that are substantiated by studies of molecular models. Also the analogy between the formic acid-formate case and the trifluoroacetic acid—trifluoroacetate case in defining Langmuir conditions may be invalid because different mechanisms are indicated by the difference in Tafel slopes.

It seems impossible to generalize from this system to others because the Tafel slope was shown to be a function of the electrode material. In studies of aqueous trifluoracetic acid--trifluoroacetate system, Conway and Dzieciuch indicated that with gold and palladium there was little hexafluoroethane and the respective Tafel slopes were 2RT/F and RT/F.

The variance in the empirical Tafel slopes indicate the complexity of the electrode reaction. The work of Conway and Dzieciuch did prove the existence of irreversibily formed thin films. This was shown by pseudo-capacitance measurements and the marked hystersis exhibited in the voltage-log current plots as illustrated in Figure 4.

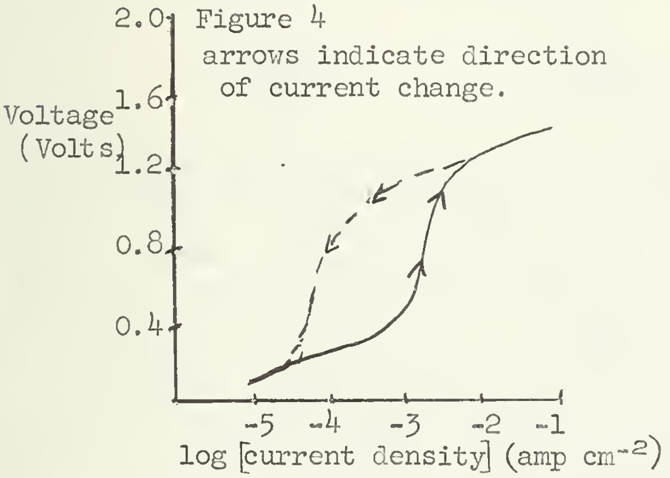


Figure 4
arrows indicate direction of current change.

This work also showed that it was not necessary to surpass the critical potential to produce Kolbe product. The authors found hexafluoroethane evolution in the lower Tafel region in anhydrous media. Since the break in the Tafel curve has been associated with the formation of the thin film, Conway and Dzieciuch concluded that carboxylate thin film formation is not necessary for Kolbe product formation in nonaqueous systems.

Analogous studies were conducted on the acetic acid-acetate system by Khomutov and coworkers and Dickenson and Wynne Jones.[15,16] Khomutov's Tafel parameters were equatable to 2RT/F, as was Conway's for formic acid, but Khomutov suggested that the electrode film was oxygen in the lower Tafel region and a metallic oxide beyond the transition region.

Dickenson and Wynne Jones, with analogous Tafel parameters, suggested the following model for the Kolbe mechanism in aqueous solutions. They considered the electrode surface to consist of many bonding sites for which the hydroxyl and carboxylate anions compete at low potentials. The hydroxyl radicals react immediately while the carboxylate anions or radicals form a film, which hinders the discharge of the hydroxyl ion and causes an overpotential. The critical potential indicates a mechanism change from O_2 evolution to Kolbe product formation and occurs when two carboxylate anions occupy the same site and Kolbe product formation precludes oxygen evolution.

All attempts to correlate empirical Tafel parameters with calculated ones have in most cases been inconclusive. Another theoretical correlation based on the standard potentials of various possible reactions has been conducted by Eberson.[18] In his study Eberson neglects all effects of the electrode surface; the potentials were calculated from thermodynamic data and are presented in Table III.

TABEL III

Standard potentials of processes possibly involved in the Kolbe electrolysis.

Electrode process (in volts)

R	$RCOO^{\ominus}/RCOO\cdot$	$R\cdot/R^{\oplus}$	$RCOO^{\ominus}/R\cdot+CO_2$	$RCOO^{\ominus}/R^{\oplus}+CO_2$	$RCOO\cdot/R^{\oplus}+CO_2$	$EtCO_2^{\ominus}/C_2H_4+CO_2+H\cdot$	$EtCO_2^{\ominus}/C_2H+CO_2+H^{\oplus}$
	XXXVII	XXXVIII	XXXIX	XL	XLI	XLII	XLIII
CH_3	2.41	2.92	1.55	2.24	2.06		
C_2H_5	2.33	2.07	1.28	1.68	1.11	1.92	0.31
nC_3H_7	2.23	2.11	1.36	1.73	1.24		
iso C_3H_7		1.59					
$t\text{-}C_4H_9$		1.27					
C_6H_5	1.66		1.90				

Eberson attempted to fit the theoretical potential values to the following Tafel equation found empirically by Vasiler and Fiochin for acetic acid.

$$E = 2.07 + 0.12 \log I - 0.12 \log A_{aco^{\ominus}} \qquad \text{XLIV}$$

This is analogous to a combination of equations XX, XVI and XVII where I is the current density and $A_{aco^{\ominus}}$ is the activity of the acetate ion. By substitution of this equation into XIII and XIV with the assumption that Cred = A_{aco^-} and with constants being replaced with numerical values equation XLIV is convertible to equation XLV.

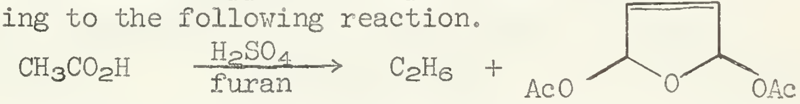
$$E = 2.01 = 0.12 \log Fk_a \qquad \text{XLV}$$

By substitution of the theoretical potentials calculated in Table III the following rates are calculated for reaction XXXVII and XXXIX.

Reaction	Rate.	E^{01}
XXXVII	10^{-2}cm/sec.	2.41v
XXXIX	10^{-9}cm/sec.	1.55v

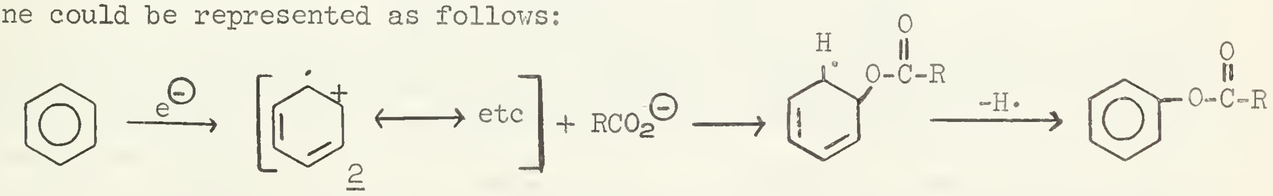
Since the reaction occurs at approximately 2.2 volts and is irreversible because Tafel slopes are applicable, Eberson indicates that reaction XXXIX if favored over XXXVII. At 2.2 volts the relative rates would be $10^{-8}$and 10^{2} respectively. For this reason, Eberson favors an irreversible one electron transfer with simultaneous bond breaking. Eberson assumes the electrode surface has no effect on the reactions and his valves for potentials are only approximate because much of the data had to be extrapolated from conditions other than standard conditions.

Hypotheses concerning the acyloxy radical as an intermediate have been abetted by the isolation of acetoxyl substituted products when trapping agents are present in the electrolysis system. Wilson and Lippincott reported the isolation of 2,5-diacetoxydihydrofuran according to the following reaction.



No methyl dihydrofurans were isolated.[19] Wilshire isolated a 25% yield of α-naphthol upon hydrolysis of the initial product formed from the electrolysis of benzoic acid in napthalene.[20]

Eberson has indicated that reactions of this type could arise from discharge of the trapping compound and subsequent attack by the anion. For example, discharge of benzene could be represented as follows:

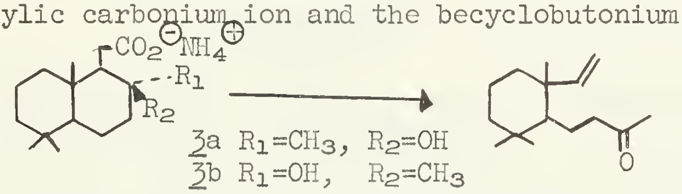


This is just one of many ways the species (2) could react to give product; it it could also react with a radical or lose a hydrogen atom to form a benzene cation. Ross, Finklestein and Petersen presented further evidence for this type of mechanism by showing that the decrease in ethane production when acetic acid is electrolyzed in the presence of aromatic compounds varied directly with the ionization potential of

the added compound. That is, the lower the ionization potential the greater the decrease in ethane evolution.[21]

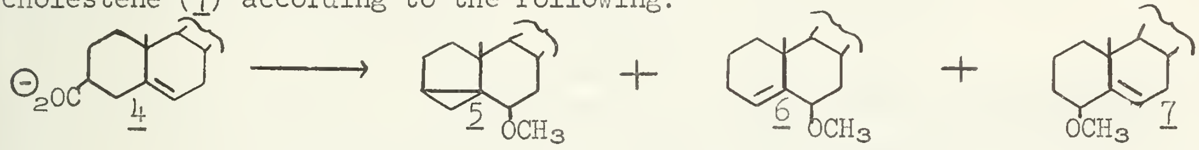
Carbonium Ion Intermediate: Eberson in his theoretical discussion indicated the possibility of carbonium ion intermediates. Although there has been much evidence for carbonium ions as intermediates only the more definitive work will be summarized here.

In order to elucidate the anomalous reaction of the following γ-lactonic moiety (3 a, b), Corey and Bauld investigated the possibility of electrolytic production of the cholesteryl homoallylic carbonium ion and the becyclobutonium ion.[22,23]

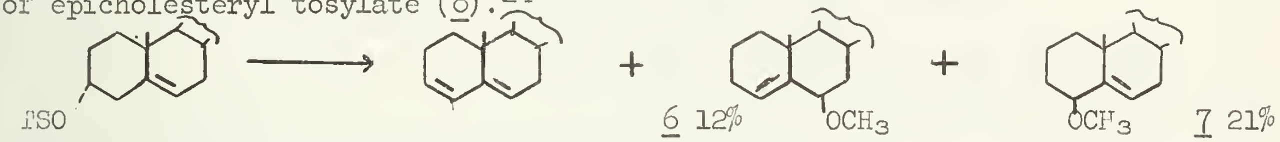


3a $R_1=CH_3$, $R_2=OH$
3b $R_1=OH$, $R_2=CH_3$

Electrolysis of Δ^5-cholestene-3β-carboxylic acid (4) in methanol at 150 V. gave 6β-methoxy-3,5-cyclocholestane, (5) 6 -methoxy-Δ^4-cholestene (6) and 4β -methoxy-Δ^5-cholestene (7) according to the following:

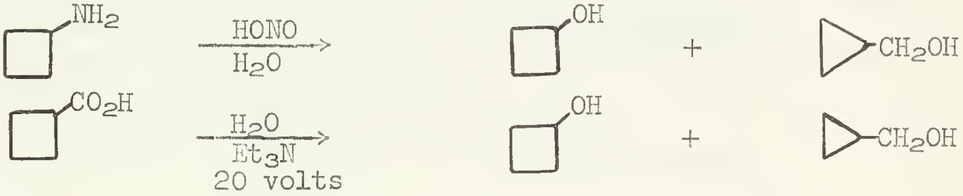


These products were analogous to those obtained by Evans and Shoppee in the solvolysis of epicholesteryl tosylate (8).[24]



The use of 150 V. by Corey and Bauld was much more drastic than the usual 5 to 10 volts used for electrolysis. This may have favored the carbonium ion.

Corey and Bauld compared the deamination of cyclobutylamine with the electrolysis of cyclobutanecarboxylic acid according to the following reactions:



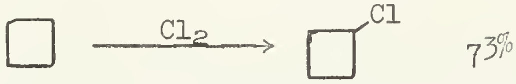
Product percentages and means of analysis are shown in Table IV.

TABLE IV.

The % product according to reaction and means of analysis.

Product	deamination-IR.	deamination-VPC.	electrolysis VPC.
cyclobutanol	51	60	53
cycloproylcarbinol	49	40	47

In contradistinction, Roberts has shown that the cyclobutyl radical did not rearrange in the vapor phase chlorination of cyclobutane.[25]



Carbonium ion products such as non-rearranged methyl ethers have been reported in the electrolysis of aliphatic acids in methanol. These would not be expected to rearrange and therefore both rearranged and non-rearranged products can be derived from carbonium ions.

Eberson has pointed out there seems to be a correlation between the ionization potential of radicals and whether the predominant mechanism will be Kolbe product formation or a carbonium ion mechanism. If the ionization potential is below 8ev, the carbonium ion seems to be favored.

Summary. A mechanism for the Kolbe reaction that consists of direct discharge of the anion with the possibility of reversible acyl peroxide formation explains the majority of experimental results. The exact nature of the electrode process, the role of the electrode surface and the system need to be explored further. No definite conclusions can be made concerning these at the present time.

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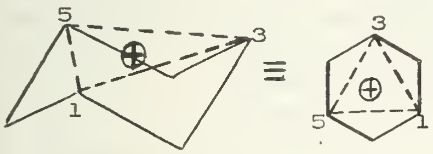
HOMOAROMATICITY

Reported by Roger A. Smith December 21, 1964

The concept "homoaromaticity" was introduced by Winstein[1,2] in 1959 to account for the unusual stability of the intermediate in the acetolysis of *cis*-3-bicyclo[3.1.0]hexyl-p-toluenesulfonate (II). This intermediate, called the "trishomocyclopropenyl cation" (I), is designated as a "homoaromatic" species by analogy with the aromatic cyclopropenyl cation[3,4]. In general the concept of homoaromaticity has been applied[2,5] to any ion or molecule which is conceptually (if not in fact) related to one of the species which fits Hückel's $(4n+2)\pi$-electron rule[6] by virtue of a methylene bridge interposed between each of the carbon atoms of the fully aromatic counterpart.

This report embraces the development of the "homoaromaticity concept." Background material under the general heading of "neighboring group participation" (including such related topics as "homoconjugation") may be found in three principal reviews[7,8,9].

The Trishomocyclopropenyl Cation

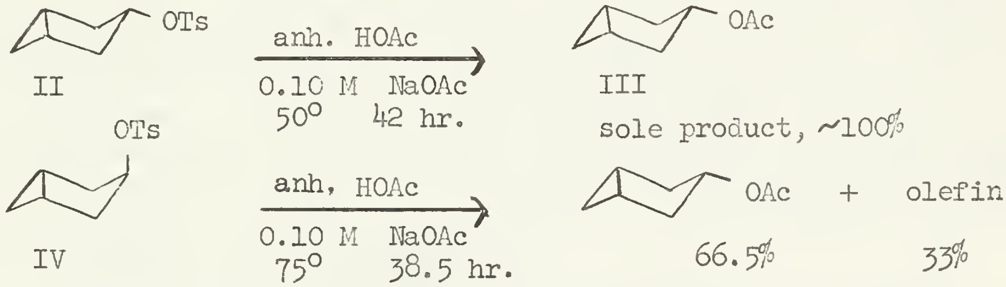


I

The data which led Winstein and Sonnenberg to postulate[1,5,10] the existence of the trishomocyclopropenyl cation (I) will be presented and discussed first. This should serve as a basis for the subsequent consideration of intermediates in the solvolysis of other 3-bicyclo-[3.1.0]hexyl systems.

The acetolysis of cis- and trans-3-bicyclo[3.1.0]hexyl tosylates[10] (Fig.1) led quantitatively to *cis*-acetate (III) from the *cis*-tosylate (II), and to the *cis*-acetate (66.5%) accompanied by olefin (33%) from the *trans*-tosylate (IV). This difference in the extent of elimination to olefin contrasts markedly with that in the acetolysis of *cis*- and *trans*-4-t-butylcyclohexyl tosylates[11], where olefin is formed dominantly in each case (*cis* → 86%, *trans* → 72%).

Figure 1 Acetolysis of 3-Bicyclo[3.1.0]hexyl Tosylates



The first-order acetolysis of each epimer (II and IV) was characterized by the "normal" salt effect[7,12] in the presence of sodium acetate. In contrast, only the *cis*-tosylate (II) displayed a definite "special" salt effect[7,13,14] in the presence of lithium perchlorate at low concentrations (4×10^{-3}M LiClO$_4$ is sufficient to introduce half of the effect[10]). The special salt effect reflects the presence of a relatively stable carbonium ion capable of forming a discrete ion pair with the perchlorate anion. The salt effects are summarized in Table 1.

Table 1 Effect of $LiClO_4$ on the Acetolysis of Several Tosylates

Tosylate	T^oC	Special Salt Effect	10^5k, sec^{-1} k_{ext^o}	k_{t^o}	k_{ext^o}/k_{t^o}
cis-3-bicyclo[3.1.0]hexyl (II)	50.0	yes	7.87	2.48	3.17
trans-3-bicyclo[3.1.0]hexyl (IV)	75.0	small-none	5.60	4.80	1.17
Δ^3-cyclopentenyl	50.0	no	0.436	0.438	0.99
cyclopentyl	50.0	no			
cyclohexyl	50.0	no			

Key: k_{t^o} is the titrimetric rate constant at zero salt concentration; k_{ext^o} is the rate constant found by extrapolating the linear ("normal") portion of the plot of k_t vs. $[LiClO_4]$ to zero salt concentration; the ratio of the two constants affords a measure of the magnitude of the special salt effect.

The rate data[10] indicate a slight anchimeric acceleration of the solvolysis of cis-3-bicyclohexyl tosylate (II) (Table 2), the usual problem of selecting a compound for comparison notwithstanding[8].

Table 2 Reactivities of Some Tosylates in Acetolysis at 50.0°

Tosylate	10^5k, sec^{-1}	k_{rel}
cyclopentyl	3.60	20
Δ^3-cyclopentenyl	0.438	2.4
trans-3-bicyclo[3.1.0]hexyl (IV)	0.266	1.5
cyclohexyl	0.179	1.0
cis-3-bicyclo[3.1.0]hexyl (II)	2.48, 7.87*	13.8, 44*

* value based on k_{ext^o} (defined in Table 1), the better lower limit of the ionization rate constant[10].

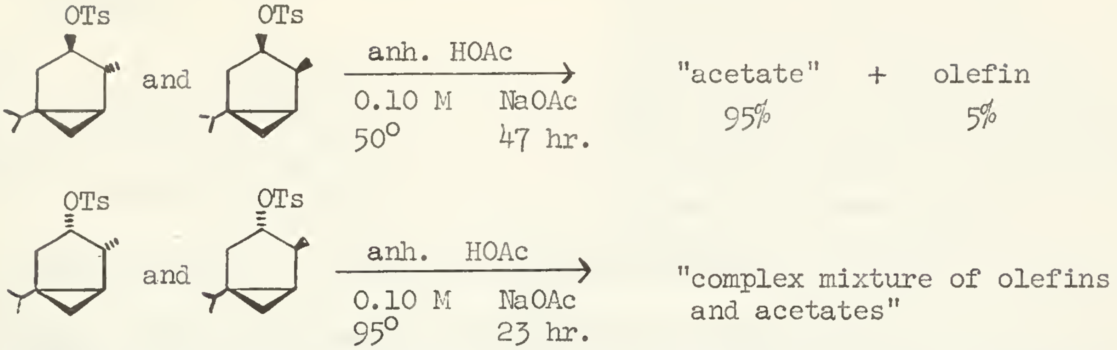
The anchimeric acceleration, stereochemistry, absence of elimination to olefin, and special salt effect observed in acetolysis suggested to Winstein[10] that ionization of cis-3-bicyclo[3.1.0]hexyl tosylate (II) leads predominantly to a unique non-classical ion, the trishomocyclopropenyl cation (I). The symmetry of I demands the equivalence of carbon atoms 1, 3, and 5. That such is indeed the case for the intermediate in the acetolysis of the cis-tosylate (II) was clearly demonstrated by Winstein and Sonnenberg[5]. Reduction of 3-bicyclo[3.1.0]hexanone with lithium aluminum deuteride, followed by chromatographic separation of the epimers, led to 98.5% pure cis- and "somehwat less pure" trans-3-bicyclohexanols. The corresponding tosylates were solvolyzed at 50.0° under conditions previously mentioned (Fig. 1). Careful analysis of the product acetates showed equal distribution of the deuterium over carbon atoms 1, 3, and 5 in that derived from the cis-3-d-3-bicyclo[3.1.0]hexyl tosylate, while no redistribution of deuterium had occurred in the solvolysis of the trans-epimer.

The deuterium scrambling results, together with the product and rate data, point forcefully toward the existence of the unique trishomocyclopropenyl cation (I) in the acetolysis of cis-3-bicyclo[3.1.0]hexyl tosylate (II). The unusual stability of I is attributed to homoaromaticity.

Before a discussion of the homoaromatic trishomocyclopropenyl cation (I) from a theoretical standpoint, evidence for the occurrence of homocyclopropenyl cations in the reactions of other systems will be presented, followed by a discussion of two papers which purport to cast doubt upon the concept of homoaromaticity, as proposed by Winstein.

The acetolysis of thujyl tosylates[15] (Fig. 2) affords some indication that products are formed in a manner analogous to that in the unsubstituted 3-bicyclo[3.1.0]hexyl system(II and IV). A thorough study of the acetolysis has not yet been reported.

Figure 2 Acetolysis of Thujyl Tosylates

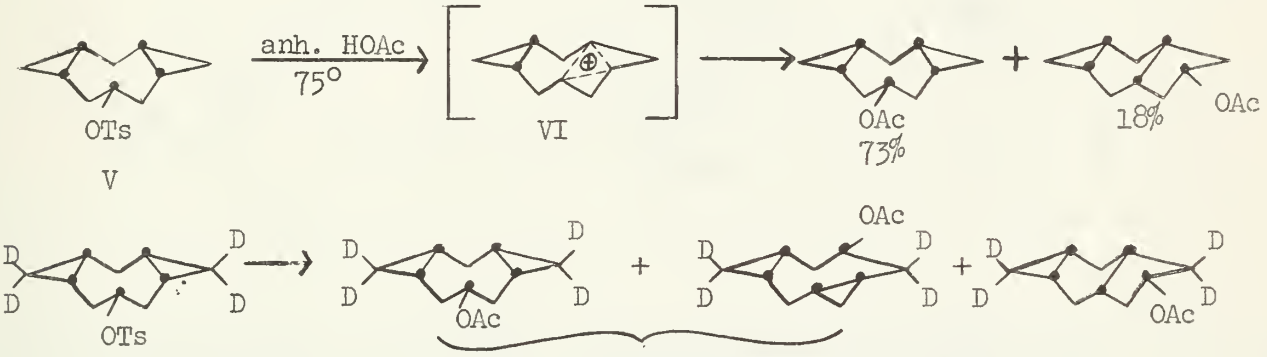

OTs
OTs
and
anh. HOAc
0.10 M NaOAc
50° 47 hr.
"acetate" + olefin
95%
5%
OTs
OTs
and
anh. HOAc
0.10 M NaOAc
95° 23 hr.
"complex mixture of olefins and acetates"

In the acetolysis of pentahomocyclopentadienyl tosylates[16,17] the rate data (Table 2), stereospecificity of acetate formation (Fig. 3) and deuterium scrambling pattern (Fig. 3) can be smoothly accommodated by the postulated bishomocyclopropenyl cationic intermediate (VI) in the solvolysis of the cis-epimer (V).

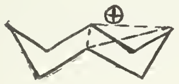
Table 2 Rates in the Acetolysis of Pentahomocyclopentadienyl Tosylates (T = 75.0°)

Tosylate	Conc.	[NaOAc]	$10^5 k$, sec^{-1}	k_{rel}
cis (V)	0.007 M	0.01 M	12.3	52
trans	0.007 M	0.01 M	0.237	1

Figure 3 Acetolysis of cis-Pentahomocyclopentadienyl Tosylate


anh. HOAc
75°
OTs
V
VI
OAc
73%
18%
OAc
D
D
D
D
OTs
D
D
D
D
OAc
OAc
D
D
D
D
D
D
D
D
OAc

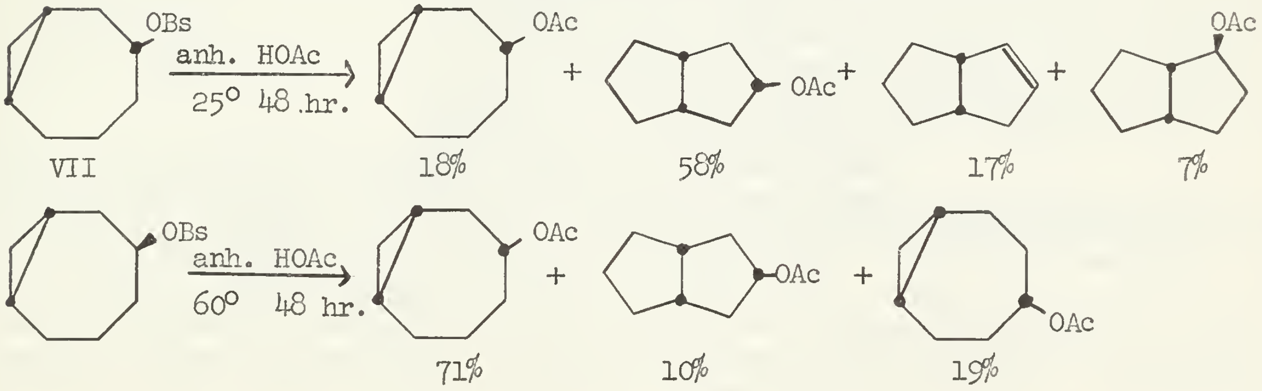
NMR: 0.52 cyclopropane CH_2 at $\tau = 10.3$



VIII

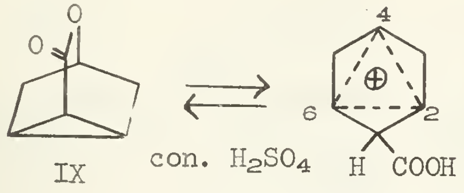
The acetolysis of cis-3-bicyclo[5.1.0]octyl brosylate (VII) (Fig. 4) has been re-interpreted[17] in terms of the non-classical intermediate (VIII).

Figure 4 Acetolysis of 3-Bicyclo[5.1.0]octyl Brosylates


OBs
anh. HOAc
25° 48 hr.
VII
OAc
18%
OAc
58%
17%
OAc
7%
OBs
anh. HOAc
60° 48 hr.
OAc
71%
OAc
10%
OAc
19%

An NMR investigation[19] of the cation generated when the lactone IX is placed in concentrated sulfuric acid indicated that the cation had a trishomocyclopropenyl structure (X) (Fig. 5). The spectrum of X showed four protons in $(AB)_2$ pattern at τ=6.91 and τ=7.10 (J=15 cps), assigned to the methylene protons, and three protons in an A_2B system at τ=6.13 and τ=6.43 (J=7 cps), assigned to the three protons at positions 2, 4, and 6; a broad peak at τ=4.59 was assigned to the proton on the carbon bearing the carboxyl group. The spectrum was unaffected when determined in D_2O/fuming sulfuric acid.

Figure 5

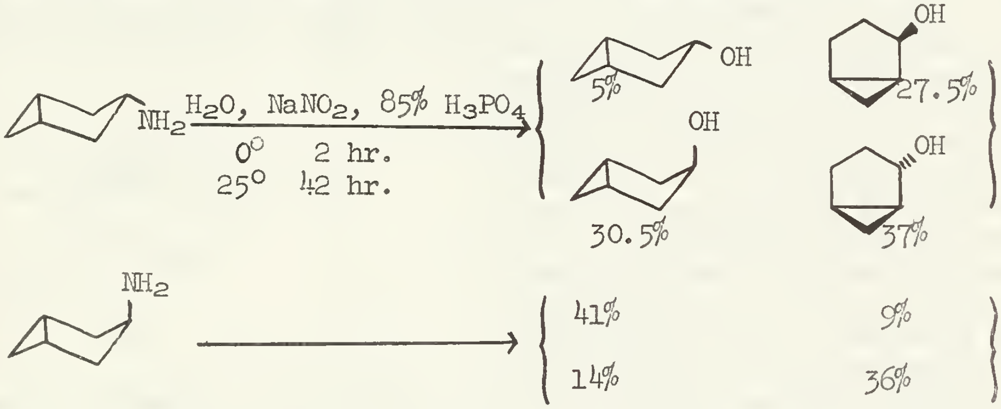


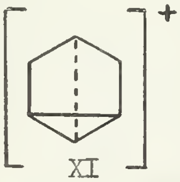
IX

X

Corey, et.al., have investigated two bicyclo[3.1.0]hexyl systems which appear not to involve the trishomocyclopropenyl cation (I). The deamination of cis- and trans-3-bicyclo[3.1.0]hexyl amines[20] (Figure 6) led to products of an entirely different countenance from those in the solvolysis of the corresponding tosylates (Fig. 1). The 3-alcohols formed in the deamination of cis- and trans-3-d-3-bicyclo[3.1.0]hexyl amines were found[20] to contain most, if not all, the deuterium at the three-position, indicating that the trishomocyclopropenyl cation (I) does not intervene. These results suggest that the trishomocyclopropenyl cation (I) is not so stable that its formation is favored in all 3-bicyclo[3.1.0]hexyl cationic systems. Indeed, in the light of these finding, Corey and Dawson[20] preferred to reconsider the nature of the cation formed in the acetolysis of cis-3-bicyclo[3.1.0]hexyl tosylate. An alternative to direct formation of the trishomocyclopropenyl cation (I) was given[20] which would involve the initial formation of the ion XI, followed by subsequent rearrangement to I or possibly to interconverting ions of lower symmetry. It would seem, however, that direct formation of I in the cis-tosylate solvolysis provides the simplest interpretation consistent with the available facts.

Figure 6 Deamination of 3-Bicyclo[3.1.0]hexyl Amines

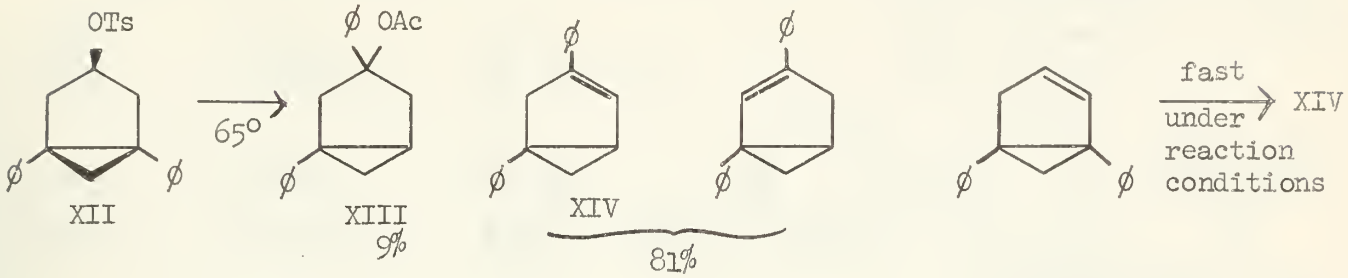




XI

It was demonstrated by Corey and Uda[21] that the acetolysis of 1.5-diphenyl-cis-3-bicyclo[3.1.0]hexyl tosylate (XII) (Fig. 7) proceeds at a rate slightly slower than that for the acetolysis of the unsubstituted cis-3-tosylate (II). This result was interpreted[21] as strong evidence against the idea of anchimerically assisted ionization of the cis-3-bicyclo[3.1.0]hexyl tosylates to give directly the trishomocyclopropenyl cation. It was expected[21] that the presence of the phenyl groups would stabilize the trishomocyclopropenyl structure considerably, since they apparently stabilize the cyclopropenyl

Figure 7 Acetolysis of 1.5-Diphenyl-cis-bicyclo[3.1.0]hexyl Tosylate



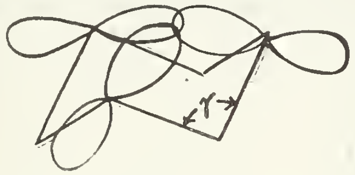
XII

XIII
9%

XIV
81%

cation[4], giving rise to an enhanced rate relative to the unsubstituted cis-3-tosylate (II). However, one would question the choice of the cyclopropenyl cation as a model compound. Unfortunately, little is known about the extent to which a phenyl group stabilizes a non-classical ion of the type in question. Hence the participation of the trishomocyclopropenyl cation in the solvolysis of XII cannot be discounted (at the present time) solely on the basis of the observed rate. It would be of interest to know if the solvolysis of XII were characterized by a special salt effect. The stereochemistry of the 1.3-diphenyl-3-bicyclo[3.1.0]hexyl acetate (XIII) was not reported.

The trishomocyclopropenyl cation (I) has been treated theoretically[22]. The cation is expected to have the chair conformation, the atomic orbitals on atoms 1, 3, and 5 overlapping in σ-π fashion such that the electron cloud involved in the three-center bonding is concentrated on one side of the molecule[5] (XV). Molecular orbital calculations were carried out as an extension of those for the homoallylic cation[22,23]. The geometry of the trishomocyclopropenyl cation depicted by XV was assumed in the calculations, as was the crude proportionality $\beta_{13} \propto S_{13}$[24]; S_{13} was evaluated with Kopeneck's tables assuming 3.09 for the effective nuclear charge. With this approach, the maximization of [delocalization energy-strain energy] led to a predicted net stabilization of 20-40 kcal./mole for $\gamma=110^\circ-85^\circ$ (if β is taken to be 20 kcal.), or 40-100 kcal./mole for $\gamma=110^\circ-85^\circ$ (for $\beta=40$ kcal.)[22]. Hence this simple MO treatment predicts stabilization for the cation (XV) if a favorable balance between delocalization and compressional (strain) energies can be achieved. The results of Winstein and Sonnenberg[5,10] lend substance to this prediction.

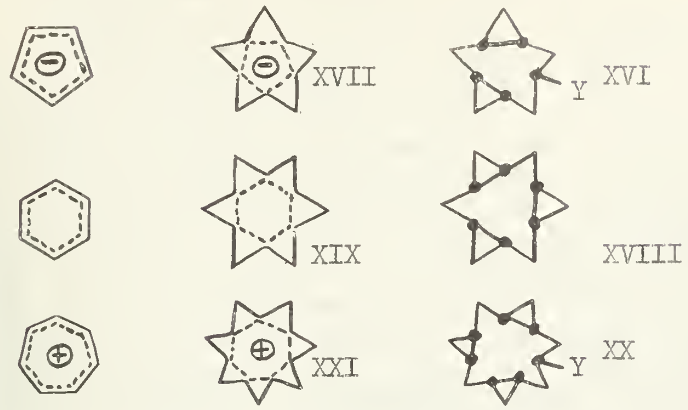


XV

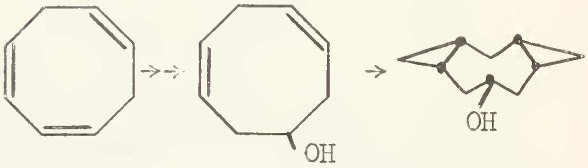
Homoaromaticity in Six-π-electron Systems

Assuming that the unique nature of the trishomocyclopropenyl cation (I and XV) is due to the delocalization of the two π-electrons in the orbital network just described, Winstein hypothesized[5] that there would exist the tendency toward such a delocalization in the "homo" analogs of π-sextet aromatic species[5,6] (Fig. 8). If a favorable balance between delocalization and strain energies could be achieved by any per-homo system, the estimated homoaromatic stability could be as much as 40% of the corresponding aromatic stabilization energy[5,23,25]. Winstein has estimated that the prospects for such a balance seem to be no more discouraging for the sextet systems than for the trishomocyclopropenyl cation.

Figure 8 Aromatic and Homoaromatic Species with π-Sextet

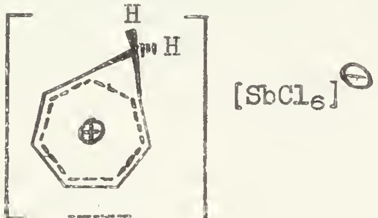


The pentahomocyclopentadienyl anion (XVII) has not yet been realized^{17}, but the parent carbon skeleton (XVI) has been made^{16}.



Hexahomobenzene (XIX) has been approached with the synthesis of tetracyclo[9.1.0.0^{3,5}0^{7,9}] dodecane (XVIII)^{26,27}. The NMR spectrum of XVIII revealed the presence of three methylene groups each having one proton cis and one proton trans to two cyclopropane rings^{27}. This preliminary evidence indicates that even in the favorable isomer (XVIII), delocalization and compressional energies do not combine to favor the postulated homoaromatic structure (XIX).

The compound which could lead to the heptahomotropylium cation (XXI) has not yet been made; progress toward its synthesis has recently been discussed by Winstein^{28}. The monohomotropylium cation (XXII) has been isolated as a stable salt^{29,30}. The NMR structure proof was unambiguous; the spectrum indicated a ring current which strongly shielded one methylene proton while deshielding the other.



XXII

Summary

The existence of the trishomocyclopropenyl cation (I) in the acetolysis of cis-3 bicyclo[3.1.0]hexyl tosylate (II) has been strongly implied, although the magnitude of its stability, and the consequent importance which must be ascribed to it in the reactions of other bicyclo[3.1.0]hexyl systems have been opened to question. Evidence has been reported for the participation of homocyclopropenyl cations in the solvolysis of other ring systems. The generalized concept of homoaromaticity as applied to π-sextet systems finds some support in the available data, but a just evaluation of the concept must await the outcome of investigations currently underway.

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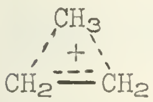
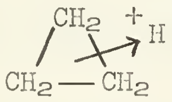
PROTONATED CYCLOPROPANE INTERMEDIATES

Reported by Nina Sussmann January 14, 1965

Introduction.--The role of protonated cyclopropane intermediates in aliphatic systems has recently been the subject of considerable controversy. There has been disagreement concerning not only the actual existence of protonated cyclopropanes as intermediates in carbonium ion rearrangements, but also the nature of such protonated cyclopropanes, three types having been variously proposed: methyl-bridged (I), π-complex (II) and hydrogen-bridged (III). This seminar will discuss the evidence concerning protonated cyclopropane intermediates in liquid phase rearrangements of simple acyclic and monocyclic carbonium ions without the special features of bicyclic structures.


I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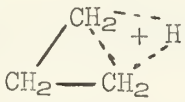
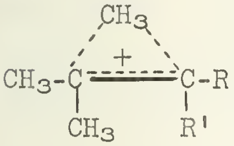

III

Methyl-Bridged Intermediates in Wagner-Meerwein Rearrangements.--For many years a growing mass of evidence indicated that methyl-bridged ions such as IVa, b and c do not figure in the reactions of carbonium ions of the neopentyl type. Moreover, arguments have been presented[3,4] that they are not important in relieving strain in highly branched molecules, as was proposed by Bartlett[5].



IVa, R=H, R'=C_6H_5 (1)
IVb, R=CH_3, R'=CH_3 (2)
IVc, R=CH_3, R'=C_2H_5 (3)

The first claim to evidence for a methyl-bridged carbonium ion was presented by Cram and McCarty[6] in an investigation of the deamination of 3-phenyl-2-butylamine (V). From threo amine was obtained alcohol, 37% of which was the product of methyl migration (1-phenyl-2-methyl-1-propanol) and from erythro-amine 6% was similarly rearranged. Of this rearranged material, 16% was optically active in the threo case and 3% in the erythro. In the optically active product the migration origin was inverted. These data support the mechanistic scheme set forth in Chart I. Although this explanation involving methyl-bridged ions VI and VII as discrete intermediates is preferred on the basis of simplicity and analogy, a second mechanistic scheme, in which the methyl bridges are transition states rather than discrete intermediates, is not excluded by the data[6].

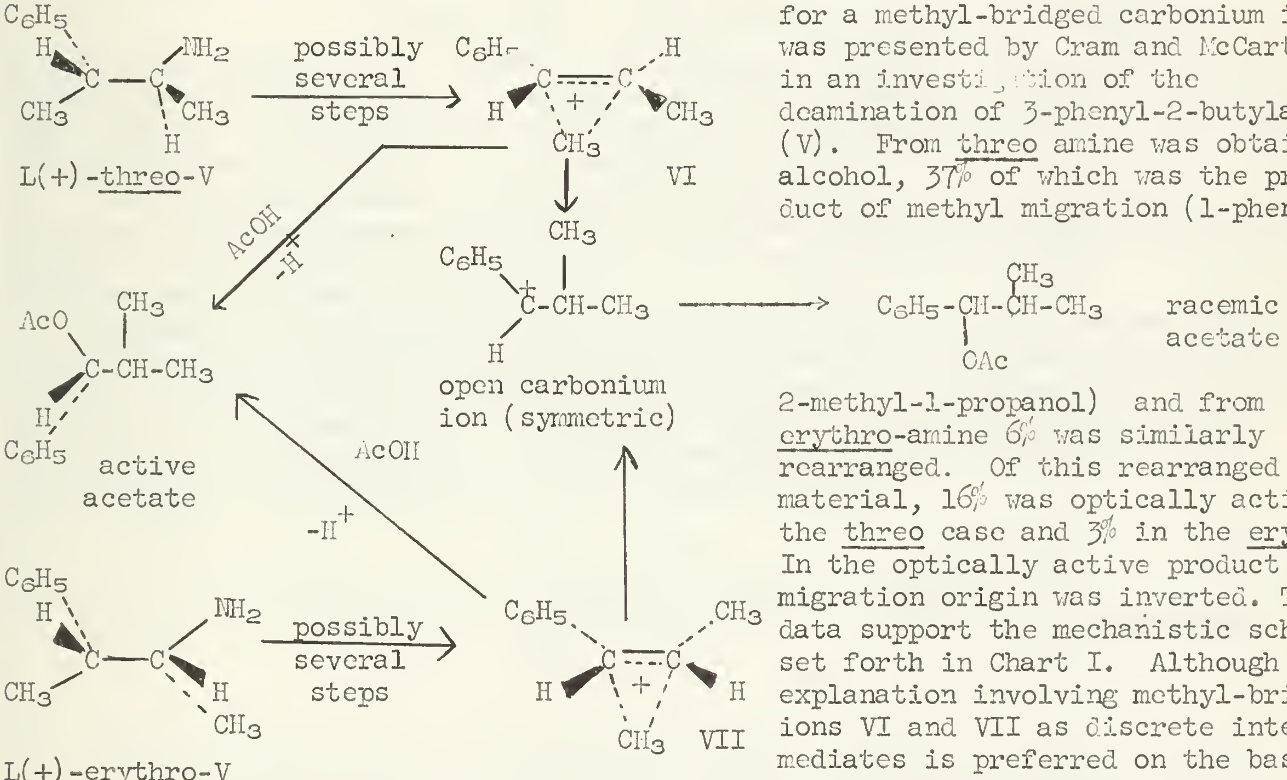
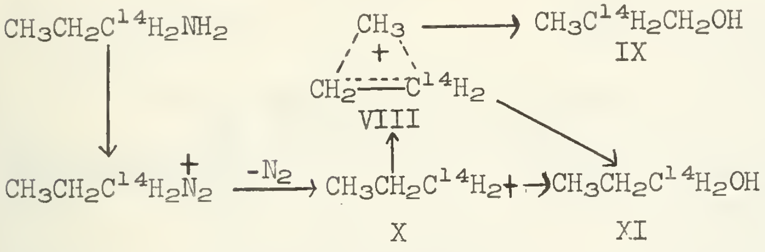


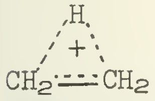
CHART I

Rearrangement of the n--Propyl Group.--In 1953 Roberts and Halmann[7] suggested that the 1-propyl carbonium ion was converted to the methyl-bridged ion VIII in the deamination of 1-aminopropane-1-C^{14} with nitrous acid at 25°. On the basis of the activity of ethylamine formed in the reactions

$$CH_3CH_2C^{14}H_2NH_2\text{-}HClO_4 \xrightarrow{HNO_2} CH_3CH_2CH_2OH \xrightarrow{KMnO_4} CH_3CH_2COOH \xrightarrow{HN_3} CH_3CH_2NH_2 + CO_2$$

the 1-propanol was believed to contain 8.5±1% of the rearranged product IX, as would be expected by having 17% of the 1-propanol originating from VIII and 83% (XI) by way of X. However, the assumption that the C^{14} was in the 2-position of the 1-propanol and adjacent to nitrogen in the ethylamine molecule lacked experimental evidence.[8] Roberts and Halmann[9] did consider the possibility that rearranged 1-propanol might arise from an intermediate such as III, but they dismissed it on the basis that the presumably more stable ion XII does not play an important role in the reaction of ethylamine with nitrous acid.[9]





XII

When the work of Roberts and Halmann was repeated by Reutov and Shatkina[8] in 1962, the 1- and 2-propanol formed by deamination of 1-aminopropane-1-C^{14} were shown to contain radioactive carbon in the 1- and 3-positions only, so that the supposed methyl migration does not, in fact, occur. Reutov and Shatkina postulated that the rearranged 1-propanol results from either a 1,3-hydride shift

$$CH_3CH_2C^{14}H_2+ \rightleftarrows +CH_2CH_2C^{14}H_3$$

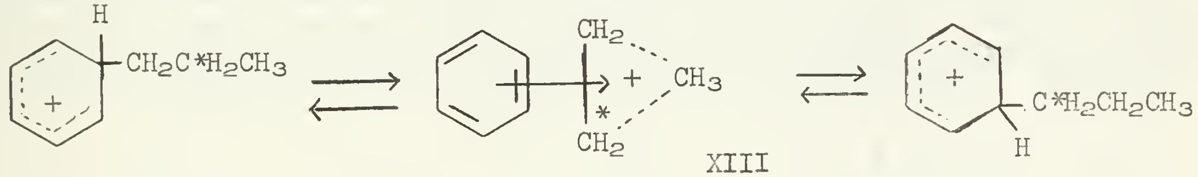
or from successive 1,2 shifts:

$$CH_3CH_2C^{14}H_2+ \rightleftarrows CH_3\overset{+}{C}HC^{14}H_3 \rightleftarrows +CH_2CH_2C^{14}H_3$$

A subsequent proton n.m.r. study of the 1-propanol formed in the deamination of 1-aminopropane-1,1,2,2-d_4 eliminated 1,2-hydride shifts and supported 1,3 shifts in the formation of 1-propanol.[10] Furthermore, it was demonstrated that the 2-propyl cation does not rearrange to the 1-propyl cation.[10,11]

The 7.5% rearrangement of $CH_3CH_2C^{14}H_2Cl$ to $C^{14}H_3CH_2CH_2Cl$ by heating at 50° for 100 hours with concentrated hydrochloric acid and zinc chloride was also postulated by Reutov and Shatkina[12] to occur by a single step hydride migration. No isopropyl chloride was detected in the reaction.

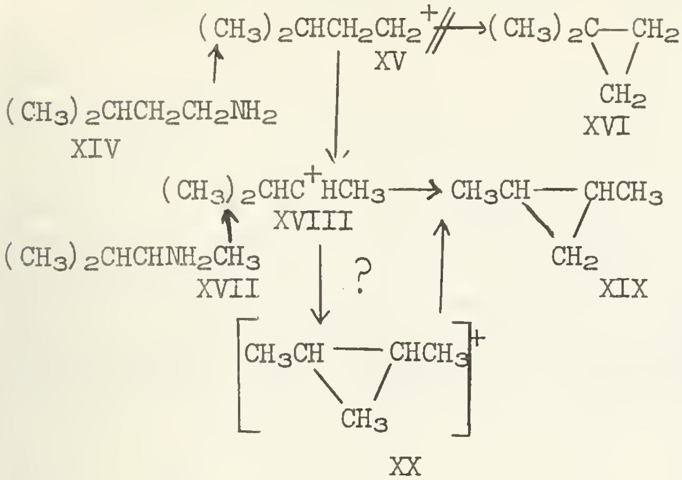
Although a methyl-bridged intermediate was excluded in the aforementioned rearrangements of the n-propyl group, it was for a while believed to be an intermediated in the aluminum chloride-catalyzed conversion of n-propyl-β-C^{14}-benzene to n-propyl-α-C^{14}-benzene without any isotope migration to the γ-position or any appreciable rearrangement to isopropylbenzene.[13,14,15] The following mechanism was proposed by R. M. Roberts and S. G. Brandenberger[14]:



XIII

In order to account for the selectivity of methyl over hydride shift, it was suggested that the special structure of the localized π-complex XIII might distinguish it from the freer carbonium ion involved as intermediate in the deamination of 1-aminopropane.[14] The interisomerization of isobutyl- and sec-butylbenzene with formation of only negligible amounts of t-butylbenzene was considered to support the proposal of the methyl-bridged π-complex intermediate.[16] However, the above mechanism was later discarded in favor of one involving phenonium ion intermediates.[17,18]

Cyclopropane Formation.--In 1960 the formation of cyclopropanes from the deamination of saturated aliphatic amines was reported for the first time by Silver.[19] In the hydrocarbon fraction from the deamination of 3-methyl-2-aminobutane(XVII) at 56° in acetic acid, cis-1,2-dimethylcyclopropane was present to the extent of 5.6% and the trans-isomer to the extent of 10.1%. The deamination of isoamylamine (XIV) gave a hydrocarbon fraction which contained 0.5% cis-1,2-dimethylcyclopropane and 1% trans-isomer and no 1,1-dimethylcyclopropane (XVI). The formation of 1,2-dimethylcyclopropane (XIX) from 3-methyl-2-butyl cation (XVIII) was explained by Silver in terms of the discrete methyl-bridged ion XX, which lost a proton to yield the cyclopropane. It was suggested that the cyclopropane formed in the deamination of isoamylamine also resulted from the 3-methyl-2-butyl cation, which was formed by hydride migration in the isoamyl cation (XV).

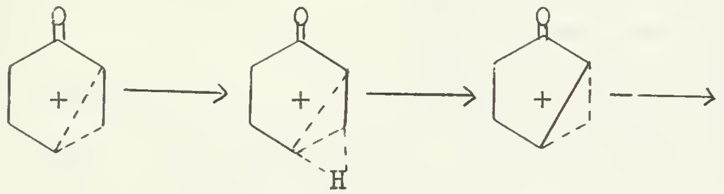


The "deoxideation" of 2-methyl-1-butanol with bromoform in a basic medium has been reported by Skell and Maxwell[20] to yield 2.1% ethylcyclopropane and 2.0% trans-1,2-dimethylcyclopropane. The formation of cyclopropane in the deamination of 1-aminopropane and in the "deoxideation" of 1-propanol has also been reported by Skell and Starer[13], both reactions giving a hydrocarbon fraction of 90% propylene and 10% cyclopropane. Because of the resemblance of the products of alcohol deoxideation to those of amine deamination, which is generally believed to proceed via carbonium ions, Skell and Starer proposed that the "deoxideation" reaction also generates carbonium ions, according to the following mechanism[21]:

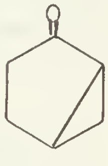
$$R\text{-}O^- + \ddot{C}Br_2 \longrightarrow R\text{-}O\text{-}\ddot{C}\text{-}Br + Br^- \qquad R\text{-}O\text{-}\ddot{C}\text{-}Br \longrightarrow R^+ + CO + Br^-$$

The cyclopropane formation was rationalized by assuming that a protonated cyclopropane, formed from the n-propyl carbonium ion, was a short-lived intermediate in the reactions.[13] However, in view of the results of Reutov and Shatkina[8], Skell and Starer later exclude a protonated cyclopropane intermediate and instead explain the formation of cyclopropane from the n-propyl carbonium ion as simply a 1,3 ring closure with loss of hydrogen ion.[11]

The disconcerting evidence that ethyl carbene, $CH_3CH_2\ddot{C}H$, produced by thermal decomposition of 1-diazopropane in aprotic media, yields the same 9:1 ratio of propylene to cyclopropane raised the possibility that the n-propyl carbonium ion is deprotonated to ethyl carbene, which cyclizes to cyclopropane. However, deoxideation of 1,1-d_2-1-propanol to give 94% dideuterated and 6% monodeuterated cyclopropane indicates that $CH_3CH_2\ddot{C}D$ is not a major intermediate in cyclopropane formation.[11]



XXI XXII XXIII XXIV



XXV

The generation of cyclopropanes has also been reported by Edwards and Lesage[22,23] in the deamination of α-aminoketones. They suggested that the first ion produced in the deamination of α-aminocyclohexanone is XXI, which is then converted by hydride migration via intermediate XXII to XXIII, followed by collapse to the classical ion XXIV, the immediate precursor of methylcyclopentenone and 3-hydroxy-2-methylcyclopentane.[23] Bicyclo-[3,1,0]-hexan-2-one (XXV) could arise by proton expulsion from XXI, XXII or XXIII.[23]

Rearrangement of Neopentyl Derivatives.--The discovery of cyclopropane formation in carbonium ion reactions stimulated interest in the protonated cyclopropane hypothesis relative to Wagner-Meerwein rearrangements.[13] Although no cyclopropane formation was reported in the deamination of neopentylamine or the deoxideation of neopentyl alcohol, protonated cyclopropane intermediates have been suggested in the rearrangement of the neopentyl carbonium ion to the *t*-amyl carbonium ion.[24]

The path of the rearrangement has been elucidated by labelling the neopentyl group at C-1 by using either the C-1-13 or the 1,1-*d*$_2$-neopentyl derivative and locating the isotope in the *t*-amyl group. Chart II summarizes the isotopic distribution predicted for possible rearrangement paths. Path a, a 1,2-methyl shift, leads to a *t*-amyl cation labelled solely at C-3; path b, involving a protonated cyclopropane of type II, distributes the label equally between C-3 and C-4.[25,26,27] Path c, a 1,3-hydride shift followed by a 1,2-methyl shift, leads to labelling of C-1 and C-4 in a 2:1 ratio, in addition to that in C-3 resulting by path a.

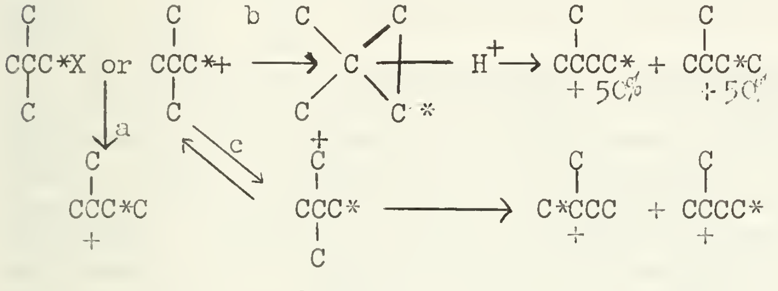


CHART II

The results of the isotopic labelling studies show that in liquid phase reactions neopentyl compounds rearrange to *t*-amyl compounds or olefins without the intervention of 1,3-hydride shifts, symmetrically protonated cyclopropanes or hydrogen-bridged ions.[25] The C^{13} distribution in the 2-methyl-2-butene and 2-methyl-1-butene resulting from deoxideation of 1,1-*d*$_2$-neopentyl alcohol with aqueous potassium hydroxide and bromoform has been examined by infrared and proton n.m.r. spectroscopies.[27] The *t*-amyl alcohols obtained from the deamination of neopentyl-1-C^{13} and neopentyl-1,1-*d*$_2$-amines, from the solvolysis of neopentyl-1-C^{13} and neopentyl-1,1-*d*$_2$-tosylates, and from the solvolysis of neopentyl-1-C^{13} iodide have been analyzed by n.m.r. and mass spectrometry.[25] In all cases the label originally present at C-1 of the neopentyl compound ends up at C-3 of the *t*-amyl compound or the olefin expected therefrom, thus supporting path a and ruling out paths b and c.

The methyl shift might proceed by synchronous C-X breaking and methyl migration, path a, or by a two step process that involves the intermediacy of the neopentyl cation, path b (Chart III). The reaction of neopentyl iodide with silver nitrate apparently goes by path b, since optically active neopentyl-1-*d*-iodide leads to inactive *t*-amyl alcohol.[25,28] Path a has been implicated by Sanderson and Mosher[28] in the deoxideation of neopentyl alcohol, because optically active 2-methyl-1-butene-3-*d* results from optically active neopentyl-1-*d*-alcohol. However, Karabatsos regards these results as equally compatible with path b, provided the methyl migration is faster than or competes favorably with rotation of the -CHD group with respect to X.[25]

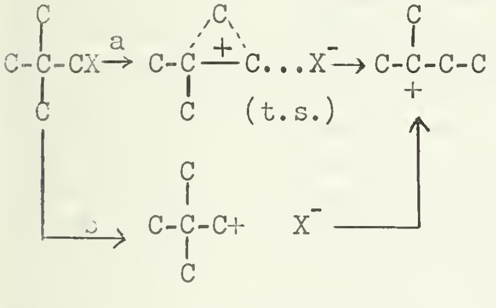
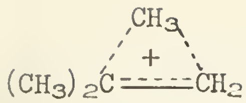


CHART III

The possibility that stereospecificity in the rearrangement could result from a methyl-bridged intermediate (XXVI), as opposed to merely a methyl-bridged transition state, has not been considered by Karabatsos. Although the isotopic labeling experiments provide evidence that a symmetrically protonated cyclopropane is not an intermediate, an unsymmetrical "edge protonated" cyclopropane is not excluded as a possibility. However, it is believed by Edwards and Lesage that such an intermediate would give rise in high yield to cyclopropane.[23]

The failure to detect 1,1-dimethylcyclopropane in the deamination of neopentyl-



XXVI

amine is not considered by Silver[29] to be a strong argument against the possibility of XXVI as an immediate precursor of olefin. Direct elimination from the methyl-bridged ion XXVI rather than from the t-amyl cation would be concordant with the low ratio of 2-methyl-2-butene to 2-methyl-1-butene relative to that observed in solvolytic reactions of neopentyl derivatives. Production of olefin from the bridged ion should greatly disfavor formation of 2-methyl-2-butene, since the two methylene hydrogens of XXVI are in a geometrically unfavorable position for elimination.[29]

Small amounts of cyclopropane derivatives have been reported in the alumina-catalyzed dehydration of three neopentyl-type alcohols: neopentyl alcohol, pinacolyl alcohol and 3,3-dimethyl-2-pentanol.[30] A mechanism involving either a methyl-bridged intermediate or a protonated cyclopropane intermediate of type II has been suggested for the cyclopropane formation, but the evidence is considered insufficient for making a choice between this mechanism and one involving concerted loss of H and OH. A methyl-bridged ion has also been suggested as an immediate precursor of rearranged olefin, anchimeric assistance by the methyl group playing a role in the initial ionization.

The Solvolysis of Cyclopropane in Deuteriosulfuric Acid.--Although Reutov[8] demonstrated that the methyl-bridged ion I cannot be involved in the rearrangement observed in deamination of 1-aminopropane-1-C^{14}, Baird and Aboderin[31] concluded that it might nevertheless be an intermediate in the formation of cyclopropane in the reaction, if it loses a proton in preference to solvolytic ring opening. This conclusion suggested to them the possibility that cyclopropane itself might protonate reversibly in competition with solvolysis. In support of their hypothesis, Baird and Aboderin report that treatment of cyclopropane with 7.5 M deuteriosulfuric acid at 25° for varying lengths of time results in mixtures of cyclopropane and monodeuteriocyclopropane plus small amounts of dideuteriocyclopropane, in addition to solvolysis products. Baird and Aboderin recognize that the occurrence of exchange could be accommodated by a variety of mechanisms in addition to that involving reversible formation of an intermediate such as I.

In 1963 the results of a study of the solvolytic ring opening of cyclopropane were interpreted by Baird and Aboderin[32] as evidence for protonated cyclopropane intermediates of type III. They observed that solvolysis of cyclopropane in 8.4 M deuteriosulfuric acid gave an average deuterium distribution of 0.38, 0.17, and 0.46 in the 1, 2 and 3 positions, respectively, of 1-propanol. On the basis of this isotopic distribution Baird and Aboderin rule out a mechanism involving a methyl-bridged ion (I), either alone or in equilibrium with isomeric methyl-bridged ions. In a mechanism involving such methyl-bridged ions, the deuterium content of the 1- and 2-positions of the 1-propanol should be identical. A system of equilibrating primary carbonium ions or an intermediate such as III alone is also considered unlikely, since it would not be expected to lead to 2-deuterio-1-propanol. Although the isotopic distribution could formally be explained by a system of equilibrating primary carbonium ions, accompanied by some Wagner-Meerwein rearrangement of the methyl group, Baird and Aboderin regard a mechanism involving primary carbonium ions as difficult to reconcile with the observed lack of isomeric products. Whereas in the deamination of 1-aminopropane the products propylene, 2-propanol and 1-propanol are found in the approximate ratio 4:4.6:1, respectively, the maximum values in the solvolysis of cyclopropane are 0.0005:0.0027:1.

Baird and Aboderin prefer the bridged-ion formulation shown in Chart IV for the solvolysis of cyclopropane. They assume that cyclopropane adds D to give initially either the hydrogen-bridged ion XXX or the methyl-bridged ion XXVII. In order to fit the experimental results, solvolytic ring opening is assumed to occur primarily with the hydrogen-bridged ions XXXVIII, XXX and XXXI rather than with the carbon-bridged ions XXVII and XXIX. Ion XXVIII would lead to 1- and 3-d-1-propanol, ion XXX to 3-d-1-propanol and ion XXXI to 2-d-1-propanol.

Baird and Aboderin tentatively suggest that the above scheme may be involved in a variety of reactions of the 1-propyl system. They postulate that the rearranged 1-propanol observed in the deamination of labelled 1-aminopropane, the rearranged

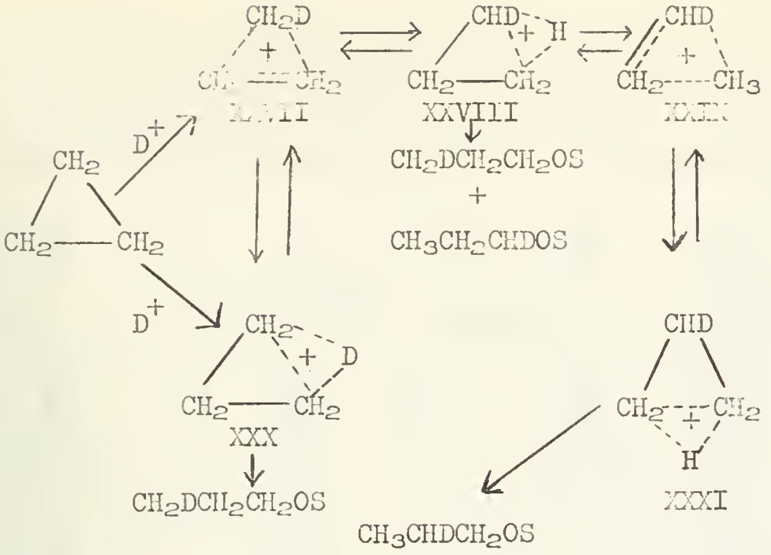
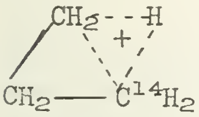
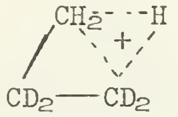


CHART IV

1-chloropropane obtained on treatment of labelled 1-chloropropane with zinc chloride, and the cyclopropane obtained in deamination, deoxideation and exchange reactions are formed by a reaction sequence of the type shown in Chart IV. According to Baird and Aboderin, the 1-propyl carbonium ion may either lose a proton, add solvent, rearrange to the 2-propyl carbonium ion or cyclize to form the hydrogen-bridged ion III. Formation of III circumvents the objections posed to the direct formation of carbon-bridged ion I. In systems where the lifetimes of the ions involved is fairly long, as in the solvolysis of cyclopropane with deuteriosulfuric acid, ion III can rearrange as shown in Chart IV, so as to account for the deuterium in the 2-position of 1-propanol.

Deamination of 1-Aminopropane.--The small amount of rearranged 1-propanol obtained in deamination of 1-aminopropane indicates that the percentage of reaction proceeding by way of bridged ions must be small.[32] By analogy with ion XXVIII in Chart IV, the ions XXXII and XXXIII, which would be formed initially in the deaminations of 1-aminopropane-1-C^{14} [18] and 1,1,2,2-$\underline{d}_4$-1-aminopropane,[10] respectively, would have to rearrange to isomeric hydrogen-bridged ions analogous to XXXI in order to lead to 1-propanol labelled in the 2-position. Since other reactions such as solvolysis and cyclopropane formation compete at each step, an extremely small amount of 2-labelled 1-propanol might be expected, as is observed.[33]


XXXII


XXXIII

Baird and Aboderin[33] have reported what they consider as evidence for the formation of cyclopropane from a protonated cyclopropane intermediate in the deamination of 1-aminopropane. Analysis by low voltage mass spectrometry of the cyclopropane formed from deamination of 3,3,3-$\underline{d}_3$-1-aminopropane under the conditions of Roberts indicates 43 ± 1% cyclopropane-$\underline{d}_2$ and 57 ± 1% cyclopropane-$\underline{d}_3$. These results are not considered by Baird to be in accord with the belief that a rearranged 1-propyl carbonium ion is responsible for the rearranged 1-propanol and the cyclopropane-$\underline{d}_3$. One might expect the loss of D in forming cyclopropane in the deamination of 1-aminopropane to reflect the extent of rearrangement (9%) observed in forming 1-propanol.[33] Thus, in deamination of 3,3,3-$\underline{d}_3$-1-aminopropane, 9% rearrangement of $CD_3CH_2CH_2+$ to $+CD_2CH_2CH_2D$, in which there is a 2:1 probability of H loss to D loss, would lead to the prediction that not more than 6% cyclopropane-$\underline{d}_3$ should be formed if there is no isotope effect on deprotonation, and no more than 31% for k_H/k_D as large as 7. The fact that the observed fraction of cyclopropane-$\underline{d}_3$ is far in excess of this amount is cited as evidence that the cyclopropane-$\underline{d}_3$ is not formed from an $\underline{n}$-propyl carbonium ion.

Baird and Aboderin claim that, if an isotope effect for proton loss of $\underline{ca}$. 2.7 to 3.0 is invoked, the above results can be readily accommodated by their mechanism, which involves equilibration of the initially formed XXXIV with isomeric methyl-bridged ions. An isotope effect of this magnitude is reasonable in view of the observed isotope effect (k_H/k_D=1.5) on the reverse reaction, protonation of cyclopropane.[33] It is noted that the lower isotope effect is for proton transfers involving the methyl-bridged ions, and the higher one for proton transfers involving the hydrogen-bridged ions. If the cyclopropane arises by proton loss from the methyl-bridged ions formed directly from XXXIV, an isotope effect of 2.7 does give the observed ratio of cyclopropane-$\underline{d}_2$ to $\underline{d}_3$. However, significant formation of cyclopropane from hydrogen-bridged ions in the deamination seems inconsistent with Baird's data.

Once formed, the methyl-bridged ions cannot be allowed to rearrange back to hydrogen-bridged ions, since XXXII and XXXIII would then be expected to rearrange to isomeric hydrogen-bridged ions analogous to XXXI, which would lead to labelling of 1-propanol in the 2-position, contrary to observation. Cyclopropane formation from unrearranged XXXIV, the only hydrogen-bridged ion thus possible, would give only cyclopropane-$\underline{d}_2$.

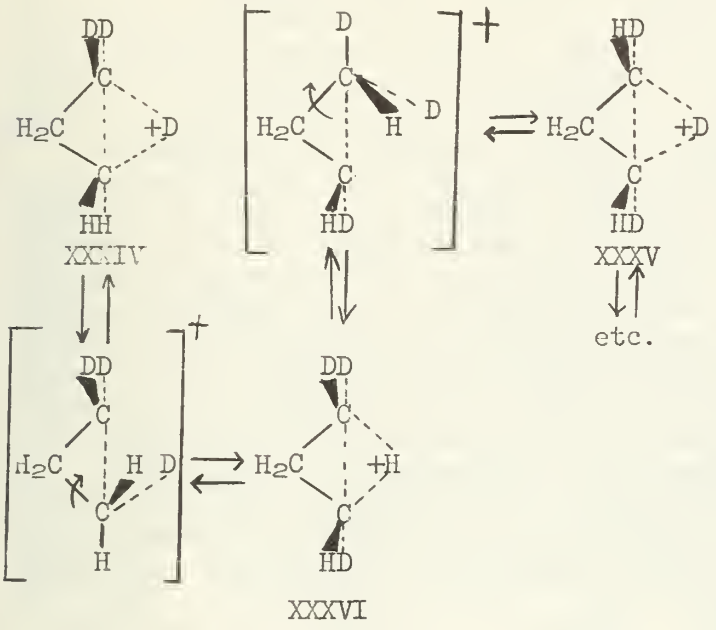


CHART V

Wiberg[34] has suggested a variation of the mechanism of Baird and Aboderin, which involves equilibration of hydrogen-bridged ions XXXIV, XXXV, XXXVI, etc., by means of methyl-bridged ions which differ from those of Baird and Aboderin in that they have a "memory" provided by a barrier to internal rotation as to which side the hydrogen was originally bridged on. According to the Wiberg mechanism, if the lifetimes of the bridged ions are sufficiently long, the deuterium and hydrogen will be statistically distributed among the five positions involved. Loss of the bridging hydrogen or deuterium would lead to cyclopropane-$\underline{d}_3$ or $\underline{d}_2$, and solvolytic ring opening to rearranged 1-propanols. The product ratio of cyclopropane-$\underline{d}_3$ to $\underline{d}_2$ would be accounted for by an isotope effect of $k_H/k_D=2.0$ for deprotonation. With longer lifetimes of the bridged ions, subsequent rearrangement to involve the remaining two hydrogens could occur by a transition state resembling the methyl-bridged ion of Baird and Aboderin.

The Wiberg mechanism accounts for the different extents of rearrangement observed by Karabatsos[10] and by Roberts[7] in the 1-propanol obtained on deamination of 1,1,2,2-$\underline{d}_4$-1-aminopropane (11.8%) and 1-aminopropane-1-C^{14} (8.5 ± 1%), since one would expect more mixing of hydrogens than of carbons in an intermediate analogous to XXXIV.[33] According to the mechanism of Baird and Aboderin, one would expect equal amounts of rearrangement. However, mechanistic conclusions derived from a comparison of the extents of rearrangement in the two deaminations should be regarded with suspicion. Baird has recently found that the rearrangement is quite temperature dependent and that the extent of rearrangement in the 1-propanol is much less (4%) than that found previously.[35]

Karabatsos[36] has recently carried out a study of the deuterium distribution in the 1-propanol obtained from nitrous acid deamination of a mixture of 1,1-$\underline{d}_2$-1-aminopropane (96.4%) and 1-$\underline{d}_1$-1-aminopropane (3.6%). The 1-propanol was converted to the trimethylsilyl ether, $CH_3CH_2CH_2OSi(CH_3)_3$, which was analyzed by mass spectrometry. The parent-less-ethyl ion gave values of 3.6% $\underline{d}_0$, 4.9% $\underline{d}_1$ and 91.5% $\underline{d}_2$, which were considered to represent the isotopic composition of the α-methylene group of the 1-propanol. Taking into account the previous finding that the rearrangement is a 1,3-hydride shift[10] permits writing the data in terms of 1-aminopropane-1,1-$\underline{d}_2$:

$$\underset{100\%}{CH_3CH_2CD_2NH_2} \rightarrow \underset{\text{XXXVII}(94.9\%)}{CH_3CH_2CD_2OH} + \underset{\text{XXXVIII}(3.6\%)}{CHD_2CH_2CH_2OH} + \underset{\text{XXXIX}(1.5\%)}{CH_2DCH_2CHDOH}$$

The abundance ratio XXXIX/XXXVIII is 0.42, whereas XXXVIII/XXXVII is only 0.038.

Karabatsos argues that if carbonium ions, XXXVII', XXXVIII' and XXXIX', were

$$\begin{tikzcd}
\underset{\text{XXXVII}'}{CH_3CH_2CD_2^{+}} \arrow[r, shift left] \arrow[d] & \underset{\text{XXXVIII}'}{^{+}CH_2CH_2CHD_2} \arrow[l, shift left] \arrow[r, shift left] \arrow[d] & \underset{\text{XXXIX}'}{CH_2DCH_2CHD^{+}} \arrow[l, shift left] \arrow[d] \\
\text{XXXVII} & \text{XXXVIII} & \text{XXXIX}
\end{tikzcd}$$

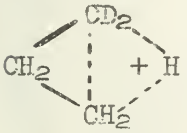
solely responsible for formation of 1-propanol, the ratio XXXIX/XXXVIII would be appreciably smaller than XXXVIII/XXXVII on account of k_H/k_D isotope effects. To account for the experimental results one would have to assume that, prior to carbonium ion capture by water, XXXVIII' and XXXIX' underwent a larger number of 1,3 shifts than XXXVII'. However, in terms of the

more generally accepted mechanism, which invokes "hot" carbonium ions as intermediates in nitrous acid deaminations, XXXVII'-the more "vibrationally excited" or unsolvated of the three-ought to rearrange more readily than XXXVIII' and XXXIX'.

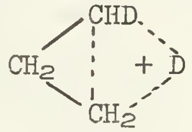
Karabatsos accounts for the results without difficulty by means of Streitweiser's[37] mechanism, which involves competition between carbonium ion formation and nucleophilic displacement on the alkyldiazonium ion. Karabatsos proposes that XXXVII arises mainly from nucleophilic displacement on the diazonium ion and XXXVIII and XXXIX from a carbonium ion intermediate, with the 1,3 hydride shifts of the propyl cation occurring faster than its capture by water.

Karabatsos considers his results to complement the finding that 3,3,3-$\underline{d}_3$-1-aminopropane leads to 57% $\underline{d}_3$- and 43% $\underline{d}_2$-cyclopropane. The same carbonium ion is believed to give rise to XXXVIII, XXXIX and cyclopropane. For simplicity of presentation this carbonium ion is pictured as the n-propyl cation, but Karabatsos' results do not permit an unequivocal choice between the n-propyl cation and a hydrogen-bridged ion.[36] In concluding that the n-propyl cation was incompatible with his experimental results, Baird assumed that XXXVII arises from the same carbonium ion intermediate as XXXVIII, XXXIX and cyclopropane. However, this assumption is untenable in the light of Karabatsos' data, which suggest that XXXVII arises mainly from nucleophilic displacement on the diazonium ion.[36]

Conclusion.--The mechanism of the deamination of 1-aminopropane is most readily interpreted as a competing direct displacement on the alkyldiazonium ion by solvent and a unimolecular fission of the diazonium ion to a carbonium ion, which can rearrange. Karabatsos' data appear inconsistent with the mechanism of Baird and Aboderin, according to which the hydrogen-bridged ion XC formed initially would have to rearrange to the isomeric hydrogen-bridged ion XCI via a methyl-bridged ion in order to give rise to XXXIX. If this rearrangement occurs, one would also expect rearrangement to XCII, which should give rise to 1-propanol labelled in the 2-position, contrary to the observations of Reutov[18] and Karabatsos.[10] Karabatsos' data also appear to be inconsistent with the Wiberg mechanism alone.[35] Statistical distribution of deuterium and hydrogen among the five positions on C-1 and C-3 of the n-propyl cation would be expected to give twice as much XXXIX as XXXVIII and three times as much XXXVIII as XXXVII. However, the available evidence is insufficient for making a choice between hydrogen-bridged ions and n-propyl cations as intermediates in the formation of rearranged 1-propanol and cyclopropane in the deamination of 1-aminopropane.[36] The rearranged products might be formed from rearranged n-propyl carbonium ions or else from hydrogen-bridged ions interconverted via n-propyl carbonium ions. A Wiberg mechanism which does not go to completion, together with some direct displacement on the alkyl diazonium ion, would also be in accord with the experimental facts.



XC



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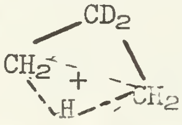

XCII

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